# BASIC RESEARCH STUDIES

**From the Society for Vascular Surgery/American Association for Vascular Surgery Research Forum**

# Differential gene expression in human abdominal aorta: Aneurysmal versus occlusive disease

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***Objective:*** **Inflammation and atherosclerosis are present in both abdominal aortic aneurysm (AAA) and arterial occlusive disease (AOD). Changes in gene expression that underlie the development of AAA versus AOD are poorly defined. This study evaluated differences in gene expression in AAA, AOD, and control aortic tissue with human gene array technology.**
***Methods:*** **RNA was isolated from human aortic specimens (seven AAA, five AOD, and five control), and complementary DNA (cDNA) probes were generated. The cDNA probes were hybridized to a human cell interaction array of 265 genes and quantitated with phosphorimaging. The data were corrected for background and were standardized to housekeeping genes. Statistical differences in individual gene expression were determined with the Kruskal-Wallis test.**
***Results:*** **Of 265 genes studied, 11 showed statistically different expression in diseased aorta as compared with control. The following three genes were downregulated in AAA: collagen VI α1 ($P < .037$), glycoprotein IIIA ($P < .006$), and α2-macroglobulin ($P < .020$). The following two genes were upregulated in AOD: laminin α4 ($P < .034$) and insulin-like growth factor 2 receptor ($P < .049$). The following three genes were upregulated in both AAA and AOD: matrix metalloproteinase–9 (MMP-9; $P < .005$), intercellular adhesion molecule–1 ($P < .012$), and tumor necrosis factor–β receptor ($P < .022$). The following three genes were downregulated in both AAA and AOD: integrin α5 ($P < .012$), ephrin A5 ($P < .037$), and rho/rac guanine nucleotide exchange factor ($P < .028$). Of 16 MMPs evaluated, only MMP-9 was significantly ($P < .005$) upregulated in both AAA and AOD. Evaluation results of four tissue inhibitors of metalloproteinases showed no significant difference in expression for all tissue types, although tissue inhibitor of metalloproteinase–1 trended toward upregulation in AAA ($P = .053$). Eight of the fifteen most highly expressed genes in all the groups were extracellular matrix or secreted proteins. Of these, only collagen VI α1 ($P < .037$) showed a significant change, although biglycan trended toward downregulation in AAA ($P = .076$).**
***Conclusion:*** **This study used cDNA array technology in the comparison of human control and pathologic aortic tissue. Six genes had similar differential expression in both AAA and AOD as compared with control. Even more interesting were differences between AAA and AOD in the expression of five genes. These data suggest a similarity in genetic expression for both AAA and AOD, with altered expression of several genes playing a role in disease differentiation.**
**(J Vasc Surg 2002;35:346-55.)**

Established risk factors for abdominal aortic aneurysm (AAA) and arterial occlusive disease (AOD) include cigarette smoking, hypertension, hypercholesterolemia, age, male sex, and family history.[1-3] AAA occurs in as much as 9% of the population of age more than 65 years and peripheral vascular disease occurs in as much as 17% of people of age 55 to 74 years in one population-based study's results.[4,5] Despite shared risk factors, peripheral vascular disease is found in less than 25% of patients with AAA.[6]

Research into the pathophysiology of AAA is difficult because the cause of the disease is multifactorial. The histopathologic hallmarks of AAA are elastin loss combined with medial and adventitial inflammation.[7] Vascular remodeling and apoptosis are present with a decreased number of vascular smooth muscle cells (VSMCs) in the media.[8] Matrix metalloproteinase–9 (MMP-9) levels are routinely elevated in AAA, and tissue inhibitor of metalloproteinase (TIMP) levels are either unchanged or increased.[9,10] AAA also has a genetic susceptibility as shown by reports of familial clustering, although no specific gene defects have yet been identified.[11,12]

Factors that underlie the development of AOD share many similarities with AAA, including common risk factors, MMP expression, genetic susceptibility, and VSMC

From the Section of Vascular Surgery, Sigfried and Janet Weis Center for Research, Geisinger Medical Center.
Competition of interest: nil.
Presented at the Fifty-fifth Annual Meeting of The Society for Vascular Surgery, Baltimore, Md, Jun 10–11, 2001.
Additional material for this article may be found online at www.mosby.com/jvs.
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0741-5214/2002/$35.00 + 0 **24/6/121071**
doi:10.1067/mva.2002.121071

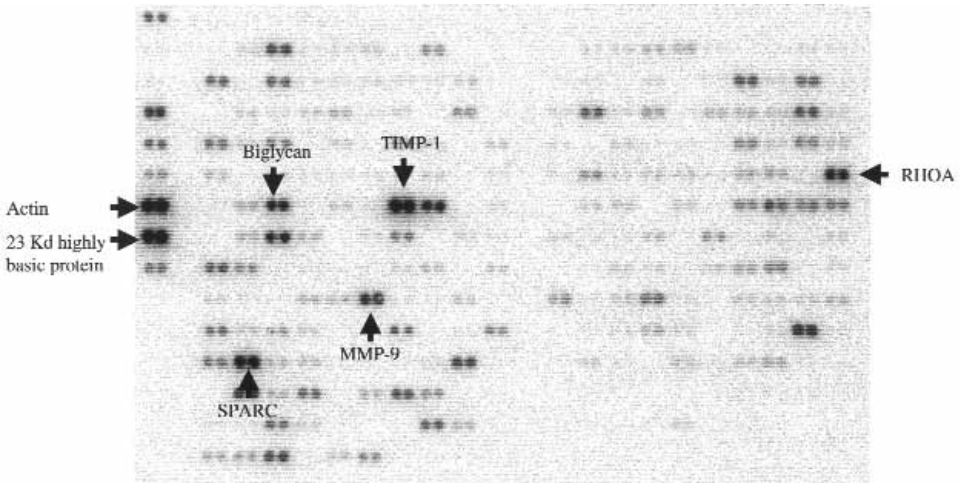


**Fig 1.** Human Cell Interaction Array (Clontech Laboratories, Palo Alto, Calif) hybridized to abdominal aortic aneurysm specimen. Housekeeping genes, such as actin and 23-kDa highly basic protein, are located in first column. Extracellular matrix proteins, such as biglycan and secreted protein acidic and rich in cysteine *(SPARC)*, are located in second to fourth columns. Other highly expressed representative genes, such as matrix metalloproteinase–9 *(MMP-9)*, tissue inhibitor of metalloproteinase–1 *(TIMP-1)*, and ras homolog gene family member A *(RHOA)* are identified.

apoptosis. The histopathologic hallmarks of AOD are proliferation of intimal smooth muscle cells within surrounding connective tissue and intracellular and extracellular lipid accumulation. MMP-9 levels are elevated in AOD as shown in carotid and aortic plaque.[13] Apoptosis of VSMC, endothelial cells, and inflammatory cells have been found in chronic atherosclerotic plaques.[14] AOD has a genetic component, as shown in family and twin studies, with several high risk genetic defects, such as familial hypercholesterolemia, having been identified.

Despite similarities underlying the development of AOD and AAA, including increased MMP-9 expression and VSMC apoptosis, these processes are not necessarily located in similar locations or in similar cells within aortic tissue. The specific types of cells and location of expression may contribute to the differentiation between AAA and AOD. The influence of multiple genetic and environmental factors may participate in the complex, multifactorial causes of these diseases.

The human genome project has allowed the sequence identification of thousands of genes. Many of these genes have unknown roles in biologic processes. An important first step in the determination of the biologic roles of these genes is the identification of differential expression in diseased versus healthy states. Previous methods used in this type of research focused on a few genes at a time and included reverse transcriptase-polymerase chain reaction (RT-PCR), ribonuclease protection assays, messenger RNA (mRNA) differential display, subtractive complementary DNA (cDNA) hybridization, and Northern blot test. A newer technique that involves hybridization of cDNA to nucleic acid arrays allows the investigation of differential expression of hundreds to thousands of genes at a time.

The objective of this study was to produce a gene expression profile of human AAA, AOD, and healthy aorta. A gene array of 265 genes that represent several families of proteins that perform structural and signaling functions was used for the evaluation of differential gene expression in AAA, aortic occlusive disease, and healthy aorta. The long-range goal was to identify factors that underlie the development of AAA and AOD.

## METHODS

Tissue from human infrarenal aorta was collected from seven patients who underwent elective open AAA repair (mean age, 71.3 ± 7.0 years; aneurysm size, 5.9 ± 0.5 cm; six men and one woman), from five patients who underwent aortobifemoral bypass grafting for AOD (mean age, 62.3 ± 6.5 years; four men and one woman), and from five organ donors (mean age, 53.8 ± 18.5 years; four men and one woman). The AAA tissue samples did not include mural thrombus and were taken from aneurysm wall devoid of mural thrombus. AAA specimens were taken from an area of aneurysmal expansion but not necessarily from the point of maximal dilatation. Specimens for AOD were all caused by flow-restricting lesions taken from areas of grossly diseased aorta. Control aortic specimens were not age-matched and were taken from infrarenal aorta grossly free of atherosclerotic disease. The Geisinger Medical Center Review Committee approved this protocol. All the patients or the families of organ donors gave written informed consent for use of the tissue for research. Aortic tissue was snap frozen in liquid nitrogen and stored at –80° before analysis.

RNA was isolated with a modified Trizol Reagent protocol (Life Technologies, Rockville, Md). Tissue was homogenized with a polytron in Trizol Reagent (50 to 100 mg of tissue/mL) and centrifuged. The supernatant was extracted with chloroform (0.2 mL/mL of Trizol Reagent) and centrifuged. The supernatant was precipitated with

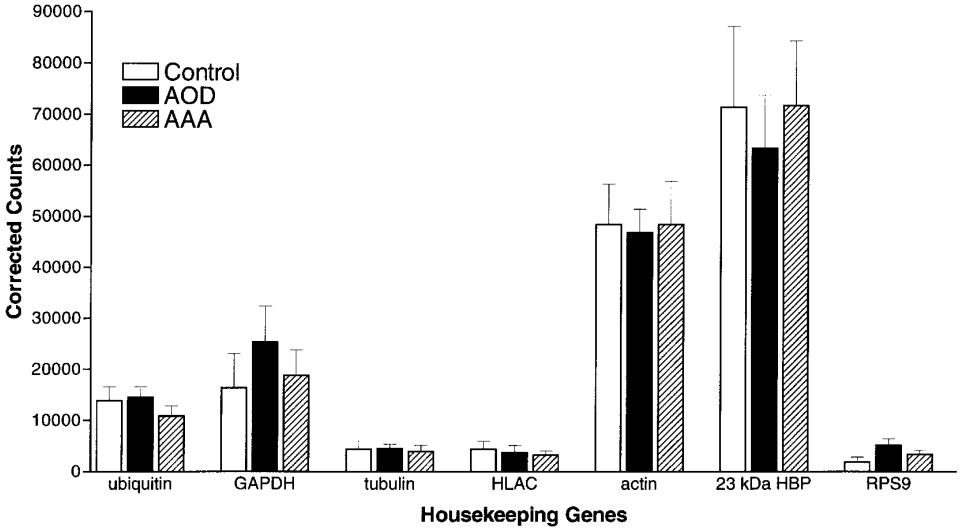


**Fig 2.** Common housekeeping genes showed consistency in expression among diseased and healthy aorta. Note should be made of increased scale of Y axis. Data are expressed as mean ± standard error of mean. *AOD,* arterial occlusive disease; *AAA,* abdominal aortic aneurysm; *GAPDH,* liver glyceraldehyde 3-phosphate dehydrogenase; *HLAC,* major histocompatibility complex class 1 C; *actin,* cytoplasmic β-actin, *23 kDa HBP,* 23-kDa highly basic protein; *RPS9,* 40S ribosomal protein S9.

isopropyl alcohol (0.5 mL/mL of Trizol Reagent) overnight at –20°C and then centrifuged. The RNA pellet was washed with 75% ethanol and dissolved in ribonuclease-free distilled $H_20$ with 0.1 mmol/L ethylenediamine tetraacetic acid. A 260 nm/280 nm absorbance ratio of less than 1.7 prompted further chloroform extraction. The RNA samples were digested with RQ1 deoxyribonuclease (Promega, Madison, Wis) followed by phenol/chloroform extraction and precipitation with ethanol and 7.5 mol/L ammonium acetate at –20°C overnight. The pellet was washed with 70% ethanol, dried with room air, and resuspended in 30 μL of $H_2O$. The yield of RNA was determined with the measurement of the absorbance at 260 nm and 280 nm. Total RNA yield and purity was evaluated with the denaturation of agarose gel electrophoresis with 1% agarose/formaldehyde gels in search of the presence of brightly stained ribosomal RNA bands.

$^{32}$P-labeled cDNA probes were synthesized with the protocol from Clontech Atlas cDNA Expression Arrays User Manual (Clontech Laboratories, Palo Alto, Calif). A set of cDNA primers specific to this array was used. The template RNA was incubated for 2 minutes at 70°C and then at 50°C. A mixture of reaction buffer, deoxyribonucleoside triphosphate mix, [α-$^{32}$P]deoxyadenosine triphosphate, dithiothreitol, and Moloney murine leukemia virus reverse transcriptase then was incubated at 50°C for 25 minutes. The reaction was stopped with 10× termination mix. The labeled cDNA products were purified with a NucleoSpin Extraction Spin Column (Clontech). Liquid scintillation counting was used for the monitoring of the incorporation of $^{32}$P.

The cDNA probes were hybridized to a Human Cell Interaction Atlas Array (Clontech). The array was prehybridized with Express Hyb solution (Clontech) and heat-denatured sheared salmon testes DNA. The labeled probe was added to denaturing solution and incubated at 68°C for 20 minutes. Neutralizing solution and $C_0$t-1 DNA were added, and the solution was incubated at 68°C for 10 minutes. New membranes with lot number 100977 were used for each specimen. Hybridization was conducted overnight with continuous agitation at 68°C. The arrays were washed with prewarmed wash solution 1 (2× standard saline citrate [SSC], 1% sodium dodecyl sulfate [SDS]; 4× 200 mL) and wash solution 2 (0.1× SSC, 0.5% SDS; 2× 200 mL) at 68°C followed by a final wash of 2× SSC (200 mL) at room temperature. The washed arrays were wrapped in plastic wrap, heat sealed in document protectors, and placed on a phosphorimager screen. The arrays were exposed to the phosphorimager screen for 16 to 24 hours. The screens were imaged with a phosphoroimager and analyzed with ImageQuant software (Molecular Dynamics, Sunnyvale, Calif).

The hybridization data were corrected for background with a calculated average for the blank columns and other blank areas located throughout the entire array. No computer manipulation was performed in an attempt to change the background scatter. Data with a signal to background ratio of less than 2.0 were excluded from further analysis. The duplicated intensity signal measurements located on the array for each gene product were summed for data analysis. The data were standardized with the four most prevalent housekeeping genes, including ubiquitin, reduced glyceraldehyde-phosphate dehydrogenase, cytoplasmic β-actin, and 23-kDa highly basic protein. These housekeeping genes were averaged for each given specimen. Comparisons were then made between specimens for the standardization of the array data.

RT-PCR was performed with 1 μg of total RNA as a template for cDNA synthesis, with random hexamers as primers in a reaction mixture containing recombinant

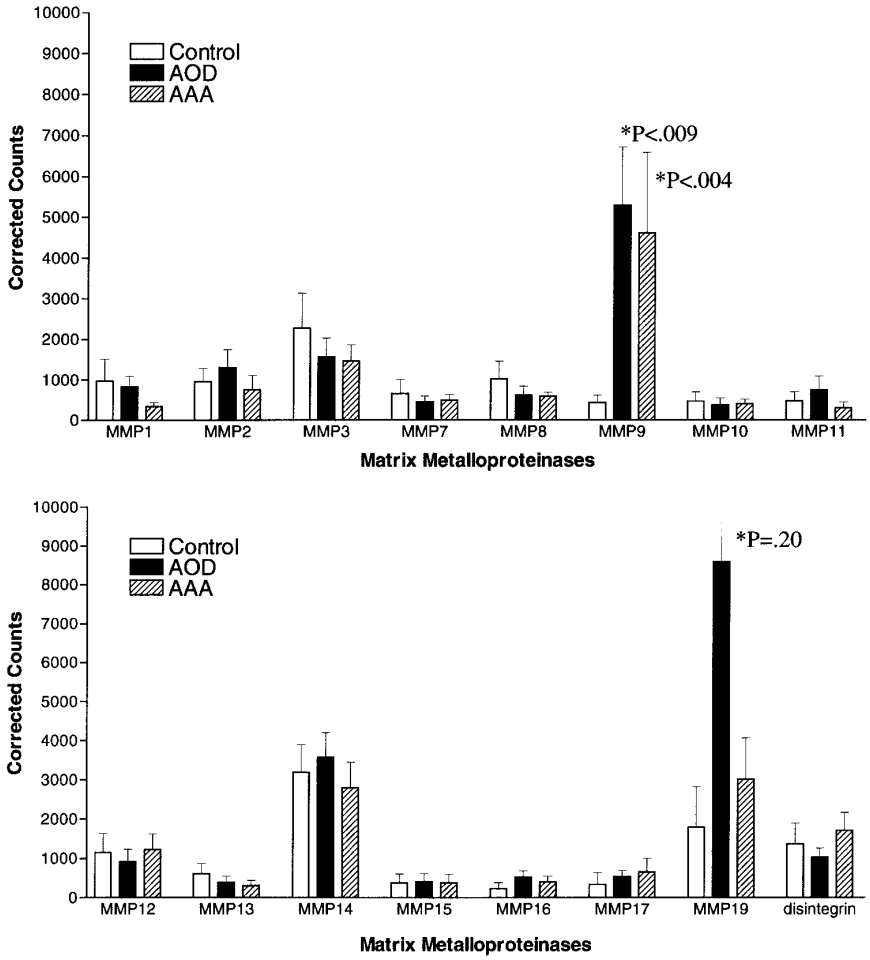


**Fig 3.** Sixteen matrix metalloproteinases *(MMPs)* had levels that were evaluated on array. MMP-9 levels were statistically elevated in arterial occlusive disease (*AOD; P* < .009) and abdominal aortic aneurysm (*AAA; P* < .004) as compared with control. No other MMPs showed statistically different expression. MMP-19, a more recently described MMP, was highly expressed in individual AOD specimens, which led to wide variation in expression and lack of statistical significance. *Disintegrin* is also known as cysteine rich protein. Data are expressed as mean ± standard error of mean.

Moloney murine leukemia virus reverse transcriptase. After enzyme inactivation, the reaction mixture was used as a template for PCR amplification. Primers were chosen with the aid of a computer program (PRIMER, Scientific & Educational Software, Inc, Durham, NC). Forty cycles of PCR amplification were carried out in a volume of 100 μL. The resulting products were separated on 1% agarose gels and stained with ethidium bromide. The product bands were identified with comparison of the observed and predicted cDNA lengths.

Statistical significance was defined as a *P* value of less than .05. Statistical evaluation included analysis of variance for three groups followed by pairwise comparisons performed with a Tukey test adjustment. In addition, statistical significance was measured with the Kruskal-Wallis test, a nonparametric test applied to more than two groups. All tests were two sided. SAS (Statistical Analysis Systems Version 8.01, Cary, NC) was used for data analysis. Data are expressed as mean ± standard error of the mean.

## RESULTS

A representative Human Cell Interaction Array (Clontech) hybridized to human AAA cDNA is shown in Fig 1. This example shows the housekeeping genes used for normalization and several other prominently expressed genes to include secreted protein acidic and rich in cysteine, an extracellular matrix protein, and ras homolog gene family member A, an oncogene. Expression of the nine housekeeping genes was remarkably similar between all tissue types, with cytoplasmic β-actin and the 23-kDa highly basic protein routinely having the highest levels of expression (Fig 2). Of the 265 genes studied, 11 showed statistically different gene expression in AAA or AOD as compared with control (Table). Of these 11 genes, six were expressed in a similar manner in both AAA and AOD as compared with control, and three were statistically different in AAA as compared with control and AOD, and two were statistically different in AOD as compared with control and AAA.

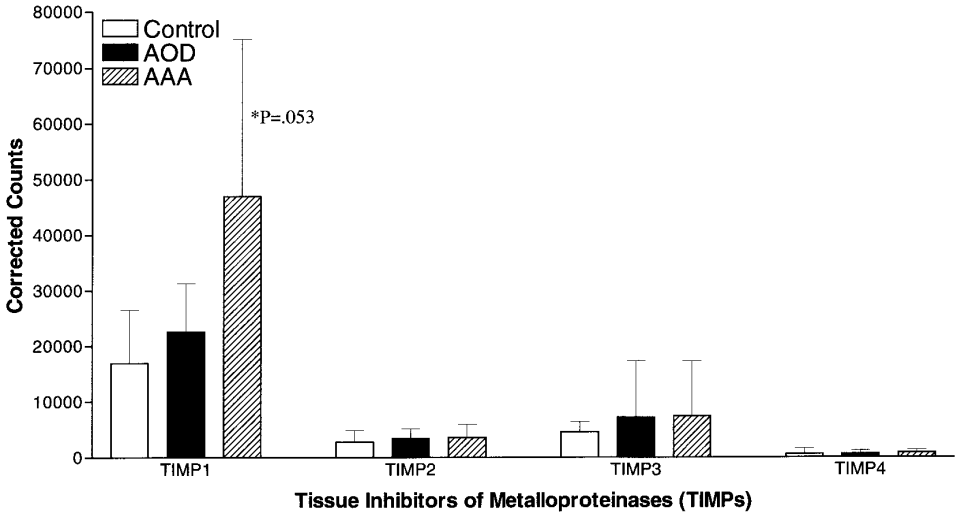


**Fig 4.** Tissue inhibitor of metalloproteinase–1 *(TIMP-1)* was most highly expressed metalloproteinase inhibitor in healthy and diseased states and trended toward upregulation in abdominal aortic aneurysm (*AAA; P* = .053). No TIMPs showed statistically different expression in healthy and diseased aorta. Note should be made of increased scale of Y axis. Data are expressed as mean ± standard error of mean. *AOD*, Arterial occlusive disease.

Sixteen MMPs were evaluated on the array. MMP-9 showed significant upregulation in both AAA and AOD as compared with control aorta ($P < .005$). The remaining MMPs revealed strikingly similar expression in all tissue types, with the exception of MMP-19, which was highly expressed in only some of the AOD specimens and did not achieve statistical significance because of this variability (Fig 3).

Eight protease inhibitors were present on the array, including TIMPs, plasma serine protease inhibitors, plasminogen activator inhibitors, and α2-macroglobulin. Four TIMPs were evaluated, and none were significantly different from control (Fig 4). TIMP-1, however, trended toward upregulation in AAA ($P = .053$). Of the remaining four protease inhibitors, α2-macroglobulin was statistically decreased in AAA but not in AOD when compared with control ($P < .020$).

Eight of the fifteen most highly expressed genes in all three study groups were extracellular matrix proteins or secretory proteins. The remaining seven of the most highly expressed genes included housekeeping genes, protease inhibitors, and oncogenes. Of the extracellular matrix genes (Fig 5), only collagen VI α1 showed a statistically significant change in expression, being downregulated in AAA ($P < .037$). Biglycan, an extracellular matrix protein, has previously been found to be decreased in AAA[15] and showed a trend toward downregulation in AAA in this study ($P = .076$). Laminin α4, another extracellular matrix protein, showed upregulation in AOD ($P < .034$).

Of 20 distinct integrins on the array, two were significantly downregulated (Fig 6). AAA and AOD showed similar downregulation of integrin α5 ($P < .012$). Glycoprotein IIIA, also called integrin β3, showed downregulation in AAA but not in AOD ($P < .006$).

Twelve genes in the tumor necrosis family or death receptor family were present on the array (Fig 7). Of this group, tumor necrosis factor–β receptor (TNF-βR), also called tumor necrosis factor receptor superfamily 1β or tumor necrosis factor binding protein 2, was statistically elevated in both AAA and AOD as compared with control ($P < .022$). No differences were seen in the other 11 tumor necrosis family genes caused by wide variability in expression.

Thirty-nine separate oncogenes or tumor suppressor genes from several different families were represented on the array. The putative rho/rac guanine nucleotide exchange factor (rho/rac GEF) or faciogenital dysplasia protein was downregulated in both AAA and AOD ($P < .028$). Insulin-like growth factor–2 receptor (IGFR-2) has been reported to be a tumor suppressor and a growth factor and chemokine receptor and was upregulated in AOD ($P < .049$).

The array contained 13 matrix adhesion receptors and 49 cell-cell adhesion receptors. Intercellular adhesion molecule–1 (ICAM-1), also known as CD 54, was statistically increased in both AAA and AOD as compared with controls ($P < .012$). Ephrin A5 was statistically decreased in both AAA and AOD ($P < .037$).

The presence of MMP-9, ICAM-1, collagen VI α1, TNF-βR, and housekeeping genes tubulin and cytoplasmic βactin was confirmed with RT-PCR in two specimens from each group.

## DISCUSSION

Gene array technology allows the evaluation of the expression of numerous genes at once, which allows identification of patterns of differential expression between healthy and diseased states. This technology results in a more efficient determination of potential targets for future research and in the identification of potential gene interactions in multifactorial diseases. Although the human

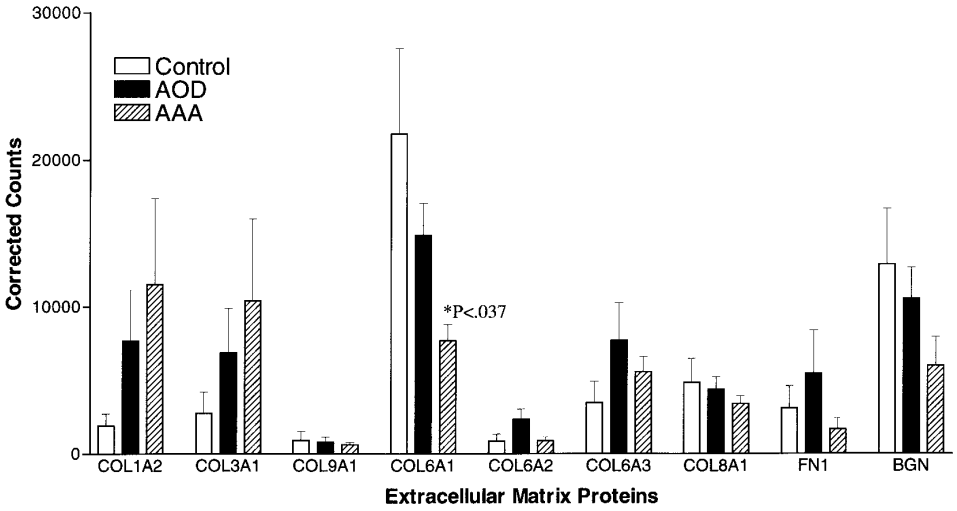


**Fig 5.** Collagen VI α1 subunit *(COL6A1)* showed significantly decreased expression in abdominal aortic aneurysm (*AAA; P* < .037). No other extracellular matrix proteins showed significantly different expression, although biglycan *(BGN)* trended toward downregulation in AAA (*P* = .076). Data are expressed as mean ± standard error of mean. *AOD,* Arterial occlusive disease; *COL1A2,* collagen I α2 subunit; *COL3A1,* collagen III α1 subunit; *COL9A1,* collagen IX α1 subunit; *COL6A2,* collagen VI α2 subunit; *COL6A3,* collagen VI α3 subunit; *COL8A1,* collagen VIII α1 subunit; *FN1,* fibronectin 1.

genome project has revealed the DNA sequences of thousands of genes, approximately half of the identified genes have no known molecular function and many other genes have not been evaluated for their role in disease.

Evaluation of human tissue from AAA, AOD, and donor aorta found 11 of 265 genes with differential expression in diseased tissue as compared with control. Interestingly, six of these 11 genes had similar expression in AAA and AOD as compared with control. Similarity in genetic expression raises the question as to a similar causative or initiating factor in these two disease processes.

**Inflammation.** Inflammation with the recruitment of lymphocytes and monocytes is invariably present in atherosclerosis and aneurysms, although it is localized in different tissue areas. Consistent with the importance of inflammation, our analysis identified upregulation of ICAM-1, TNF-βR, and MMP-9 in AAA and AOD.

ICAM-1 promotes leukocyte adhesion to and migration through endothelial cells.[16] Endothelial expression of ICAM-1 is increased in inflammation, atherosclerosis, and AAA.[17-19] The stimulus for upregulation of ICAM-1 in AAA and AOD is presently unknown.

TNF-βR is one of two known tumor necrosis factor membrane receptors. TNF-βR has been linked to regulation of proliferation, cytokine production, and apoptosis.[20,21] A correlation between ICAM-1 and TNF-βR has been shown in autoimmune diseases.[22] TNF-βR has also been associated with insulin resistance, hyperlipidemia, hypertension, autoimmune disease, and obesity.[23-27] Several of these associations are known risk factors for AAA and AOD.

MMP-9 is an extracellular endopeptidase that degrades elastin and type IV collagen.[9] In addition, MMP-9 plays a role in the proliferation and migration of VSMCs into the intima.[28] MMP-9 is increased in AAA and AOD.[8,9,13,29] In AAA, MMP-9 is localized to the adventitia and adventitial side of the media as compared with AOD, in which it is restricted to the intimal side of the media.[13] MMP-9 levels are decreased with doxycycline and nonsteroidal antiinflammatory drugs,[30,31] and the inhibition of MMP-9 activity decreases aneurysm formation in the rat model.[30,32] Data from our laboratory have documented increased MMP-9 levels in AAA through evaluation with RT-PCR and Northern blot test that are consistent with the gene array data from this study.[29]

**Protease inhibitors.** The biologic importance of MMPs may be offset if the levels of their respective protease inhibitors are altered. This study found no statistically significant difference in TIMPs expression in either AAA or AOD, although TIMP-1 trended toward upregulation in AAA (*P* = .053).

α2-Macroglobulin, a protease inhibitor and cytokine carrier synthesized in the liver,[33] was significantly decreased in AAA but not in AOD, although no change was noted in the α2-macroglobulin receptor or its associated protein. It is an elastase inhibitor and enhances transforming growth factor β1–induced VSMC growth response.[34,35] Decreased α2-macroglobulin could contribute to the increased destruction of the extracellular matrix and the decreased number of VSMCs seen in AAA.

**Extracellular matrix proteins.** Extracellular matrix destruction and remodeling is a component of both AAA and AOD. Several distinct differences in extracellular matrix proteins were noted in this study to include downregulation of collagen VI α1 in AAA and upregulation of laminin α4 in AOD.

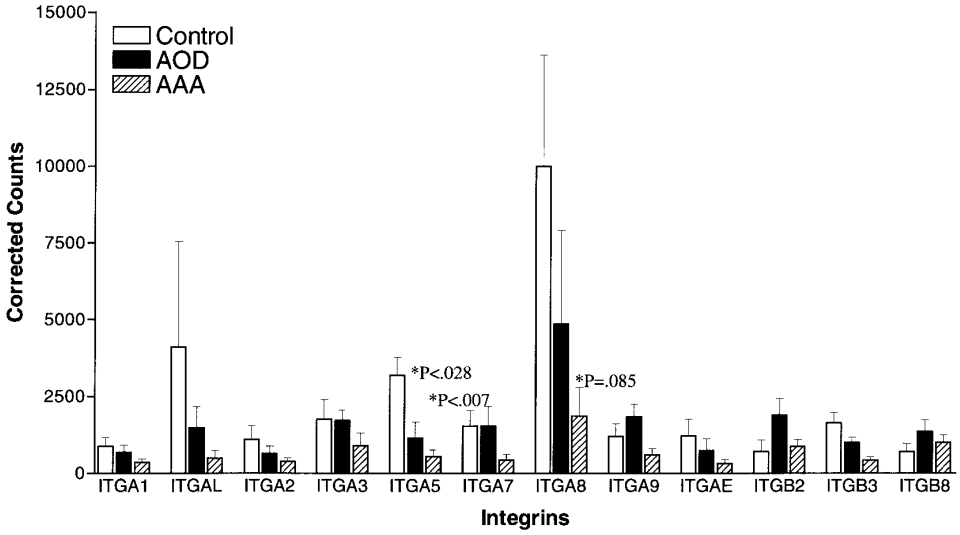


**Fig 6.** Integrins are involved in cellular adhesion and cell-matrix adhesions. Of numerous integrins evaluated, integrin α5 *(ITGA5)* only was decreased significantly in arterial occlusive disease (*AOD; P* < .028) and abdominal aortic aneurysm (*AAA; P* < .007). Remaining apparent integrin differences failed to reach statistical significance. Data are expressed as mean ± standard error of mean. *ITGA1,* Integrin α1; *ITGAL,* integrin αL; *ITGA2,* integrin α2; *ITGA3,* integrin α3; *ITGA7,* integrin α7; *ITGA8,* integrin α8; *ITGA9,* integrin α9; *ITGAE,* integrin αE; *ITGB2,* integrin β2; *ITGB3,* integrin β3; *ITGB8,* integrin β8.

Statistically significant differential gene expression

| *Increased in both groups* | | | *Decreased in both groups* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *AAA* | *AOD* | | *AAA* | *AOD* | *Increased only in AOD* | | *Decreased only in AAA* | |
| MMP–9 (*P* < .005) | 11 to 1 | 12 to 1 | Integrin α5 (*P* < .012) | 1 to 6 | 1 to 3 | Laminin α4 (*P* < 0.34) | 3 to 1 | Collagen VI α1 (*P* < .037) | 1 to 3 |
| ICAM-1 (*P* < .012) | 3 to 1 | 4 to 1 | Ephrin A5 (*P* < .037) | 1 to 6 | 1 to 3 | IGFR-2 (*P* < .049) | 3 to 1 | Glycoprotein IIIA (*P* < .006) | 1 to 4 |
| TNF-βR (*P* < .022) | 5 to 1 | 4 to 1 | Rho/rac GEF (*P* < .028) | 1 to 11 | 1 to 6 | | | α2-macroglobulin (*P* < .020) | 1 to 2 |

Comparison of abdominal aortic aneurysm and arterial occlusive disease as compared with control. Ratios represent standardized gene expression.
*AAA,* Abdominal aortic aneurysm; *AOD,* arterial occlusive disease; *MMP-9,* matrix metalloproteinase–9; *ICAM-1,* intercellular adhesion molecule–1; *TNF-βR,* tumor necrosis factor–β receptor; *IGFR-2,* insulin-like growth factor–2 receptor; *rho/rac GEF,* rho/rac guanine nucleotide exchange factor.

Collagen VI α1 is one of three chains that form the collagen type VI triple helix, which is thought to play a role in bridging cells with the extracellular matrix.[36] It serves as an anchoring element between collagen I, collagen III, elastin, and basement membrane and, in combination with fibrillin 1, is involved in VSMC and elastin contact.[37] In addition, collagen VI is the primary extracellular matrix protein responsible for von Willebrand factor–dependent platelet adhesion and aggregation, and it modulates the hemostatic response to vascular injury.[38-40] Decreased levels of collagen VI in AAA could contribute to the poor tissue tensile strength.

Biglycan is an extracellular matrix protein that interacts with collagen type VI and has previously been shown to be decreased in AAA.[15] This study did not find a statistically significant decrease in biglycan in AAA but did show a trend toward downregulation (*P* = .076). Biglycan may be responsible for trapping lipoproteins in the arterial wall.[41]

Laminin α4 is part of the laminin family of large heterotrimeric proteins with cell adhesive and signaling properties and was significantly increased in AOD. Laminins are a major component of vascular basement membranes.[42] Sphingomyelinase, an enzyme implicated in atherogenesis, adheres to laminins in the extracellular matrix of cultured smooth muscle cells.[43]

**Cellular adhesion.** The integrin family is a group of related heterodimers involved in cell-cell and cell-matrix adhesion. Integrin α5, a subunit of the fibronectin receptor (integrin α5β1), was decreased in AAA and AOD. Interestingly, Tung, Lee, and Thompson[44] found a decrease in integrin β1 in their recent gene array evaluation of AAA. Integrin α5β1 mediates cell adhesion to fibronectin[45] and transduces mechanical stimuli into intracellular signals.[46,47] In the absence of attachment to fibronectin, integrin α5β1 activates a pathway that leads to decreased proliferation.[48] Integrin α5β1 allows VSMC adhesion and migration and is a fibrinogen receptor on vascular endothelial cells.[49]

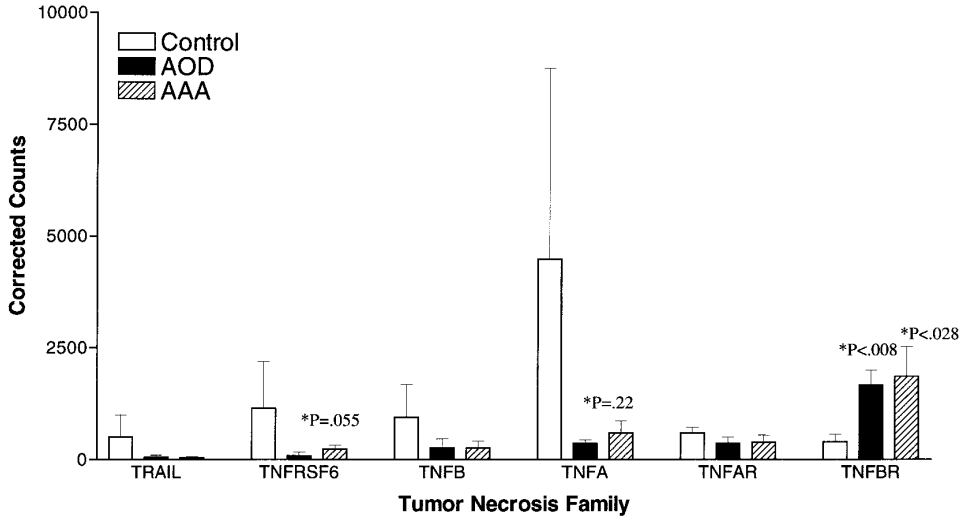


**Fig 7.** Tumor necrosis factor–β receptor *(TNFBR)*, one of two TNF receptors, was statistically increased in arterial occlusive disease (*AOD; P* < .008) and abdominal aortic aneurysm (*AAA; P* < .028). Remaining TNF family genes showed trend toward decreased expression in diseased tissue, although expression was widely varied within healthy controls. Data are expressed as mean ± standard error of mean. *TRAIL,* TNF-related apoptosis inducing ligand; *TNFRSF6,* fas antigen; *TNFB,* TNF-β; *TNFA,* TNF-α; *TNFAR,* TNF-α receptor.

Platelet membrane glycoprotein IIIA is a subunit of the platelet integrin receptor IIB-IIIA, which is responsible for the binding of fibrinogen to platelets, which leads to platelet cross-linking and aggregation.[50] Glycoprotein IIIA was significantly decreased in AAA ($P < .006$). Glycoprotein IIIA is also expressed in vascular endothelium where it mediates VSMC proliferation. A glycoprotein IIIA polymorphism has been associated with increased progression of atherosclerosis in the abdominal aorta.[51]

**Tumor suppressor genes.** Rho/rac GEF stimulates fibroblasts to form cytoskeletal elements and activates a signaling cascade that regulates cell growth and differentiation.[52,53] Expression of rho/rac GEF was downregulated in both AAA and AOD. The role of this gene in vascular biology is unknown.

IGFR-2 showed decreased expression in AOD. IGFR-2 regulates IGF-2 concentration by leading to its rapid degradation in the cell.[54] Loss of IGFR-2 or its function may be associated with a wide range of malignant diseases.[55] The role of IGFR-2 in vascular biology is unknown.

**Comparison study.** The recent paper by Tung, Lee, and Thompson[44] used an array from Clontech that contained 1176 gene probes to compare expression in AAA versus healthy aorta. Our data confirm the upregulation of MMP-9 and ICAM-1 expression in AAA noted in their paper. In addition, our data demonstrate that increased expression of these gene products is not unique to AAA but is also observed in aortic occlusive disease. Two other genes reported by Tung, Lee, and Thompson[44] to have increased expression in AAA, integrin alpha L and decorin, were not increased in our AAA or occlusive samples. TNF-βR expression, which we found to be increased, was not reported to be increased by Tung, Lee, and Thompson.[44] These differences could reflect the different data analysis methods used in the studies or could reflect actual differences that could be dependent on the patients examined in each study. Intragroup variability in gene expression in patients with AAAs could reflect differences in AAA cause or aneurysm stage. Interestingly, Tung, Lee, and Thompson[44] reported a decrease in integrin β1 expression in AAA, whereas our data identified a decrease in integrin α5 expression in AAA and AOD. Integrin α5 and integrin β1 are both components of the fibronectin receptor. We also found decreased expression of several genes, including ephrin A5, rho/rac GEF, collagen VI α1, and α2 macroglobulin, that were not represented on the array used by Tung, Lee, and Thompson.[44]

**Technical considerations.** Gene array analysis provides a powerful tool for the investigation of disease mechanisms. As with any research tool, however, some limitations of this technology exist. Although mRNA levels and tissue protein levels generally correlate, mRNA levels may not directly correlate with protein levels in the tissue as a result of posttranscriptional regulation. Further, this technique does not measure covalent protein modifications, such as phosphorylation, that can alter protein functional activity. This technique measures relative levels of mRNA that may be sufficiently active at a basal level to produce a critical protein product without being expressed differently from healthy tissue.

This technique measures the mRNA levels from harvested tissue at the end stage of the disease process. Evaluation of tissue harvested at different stages in the disease process could alter the information that is obtained. This tissue heterogeneity may lead to variability in gene

expression within a specific disease. Problems with heterogeneity and variable expression within groups may be decreased with the performance of a careful statistical analysis rather than the assumption that a given signal ratio determines significant differential gene expression. Despite limitations, this technology serves as an efficient means for the determination of potentially important targets for future research into a particular disease process.

## CONCLUSION

This study reports the use of cDNA array technology in the comparison of human control and pathologic aortic tissue. Six genes had similar differential expression in AAA and AOD as compared with control. Three of these genes are involved in inflammation, and all were upregulated in AAA and AOD. Genes that were downregulated in AAA and AOD had variable functions that included cell-cell adhesion, intracellular signal transduction, and tumor suppression. Differential expression in AAA alone revealed decreased levels of a collagen VI subunit, a protease inhibitor, and a mediator of VSMC proliferation. It is interesting that these genes may play roles in the extracellular matrix degradation and VSMC loss typical of AAA. Differential expression in AOD showed increased levels of an extracellular matrix protein and growth factor regulator. These data show major similarities in gene expression patterns for both AAA and AOD. These data provide for interesting new avenues of research into the causative factors of AAA and AOD.

## ONLINE SUPPLEMENT

The corrected count data for all specimens are available as an online supplement at www.mosby.com/jvs. The available data are listed in three tables (online only) and have been corrected for background and standardized by housekeeping genes. The identification of the gene products is with row and column. The rows correspond to the lettered rows on the Clontech Human Cell Interaction Array, with row 1 being the letter A and so on. For example, R1C1 corresponds to row A column 1 and R7C8 corresponds to row G column 8. Columns 2 and 13 have been deleted from the data because no probes were present in these columns. The gene probes may be identified at the Clontech website at http://atlasinfo.clontech.com and with the link for AtlasInfo and then Human Cell Interaction Array.

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Submitted Jul 11, 2001; accepted Oct 4, 2001.

*Additional material for this article may be found online at www.mosby.com/jvs.*

Please see the related commentary by Drs Thompson, Absi, and Tung on pages 403-4.

**Table E I, online only.** Gene array data for AAA specimens

| *Name* | *Spec AAA1* | *Spec AAA2* | *Spec AAA3* | *Spec AAA4* | *Spec AAA5* | *Spec AAA6* | *Spec AAA7* | *Avg AAA* |
|---|---|---|---|---|---|---|---|---|
| GRID- 1-R1C1 | 17396.75152 | 14718.78547 | 9736.85361 | 3899.491639 | 15549.97327 | 5543.13538 | 9014.239303 | 10837.02963 |
| GRID- 1-R2C1 | 3964.903204 | 0 | 618.7536465 | 1468.06318 | 410.6862482 | 45.52653077 | 971.5317128 | 1068.494611 |
| GRID- 1-R3C1 | 2291.613172 | 895.2946496 | 726.4531775 | 2124.667898 | 1492.294371 | 0 | 342.3200304 | 1124.662991 |
| GRID- 1-R4C1 | 29761.40479 | 31788.17924 | 3611.318233 | 18420.67577 | 33090.58938 | 13084.89949 | 2080.212181 | 18833.89136 |
| GRID- 1-R5C1 | 9293.698183 | 5756.089566 | 1402.822315 | 3246.951124 | 1693.317679 | 5281.309428 | 1255.91768 | 3990.013942 |
| GRID- 1-R6C1 | 6218.172922 | 217.5807914 | 1367.773206 | 5841.967558 | 3078.695818 | 3462.491426 | 2671.392049 | 3265.43813 |
| GRID- 1-R7C1 | 48814.28175 | 55074.6406 | 17721.07557 | 78219.89711 | 54937.10026 | 64586.4179 | 18958.15679 | 48330.20978 |
| GRID- 1-R8C1 | 51385.95835 | 48418.39468 | 118930.7528 | 49459.93767 | 46422.33615 | 66785.54723 | 119947.3918 | 71621.4526 |
| GRID- 1-R9C1 | 3812.670118 | 2722.59372 | 1460.142029 | 6394.425172 | 2156.597847 | 5526.847337 | 1691.748455 | 3395.002507 |
| GRID- 1-R10C1 | 328.6807298 | 0 | 462.6146737 | 2231.78324 | 256.7927884 | 0 | 471.78828 | 535.9512266 |
| GRID- 1-R11C1 | 160.4802515 | 0 | 617.1978506 | 2508.103377 | 208.1328764 | 0 | 393.3166999 | 555.3185556 |
| GRID- 1-R12C1 | 605.8300676 | 0 | 547.0297095 | 2452.087396 | 239.2299767 | 0 | 469.9616744 | 616.3053614 |
| GRID- 1-R13C1 | 342.8385805 | 3617.589388 | 494.4123441 | 2116.509048 | 213.0678173 | 0 | 440.6197168 | 1032.147818 |
| GRID- 1-R14C1 | 371.7912405 | 0 | 534.2512065 | 2362.720596 | 253.4498888 | 0 | 349.9314485 | 553.1633169 |
| GRID- 1-R15C1 | 513.022316 | 0 | 529.3216061 | 2483.01796 | 283.6676864 | 0 | 348.2632386 | 593.8987942 |
| GRID- 1-R1C3 | 76.44515583 | 0 | 337.4168096 | 54.58818247 | 0 | 0 | 0 | 66.92142962 |
| GRID- 1-R2C3 | 1399.06057 | 71.14468104 | 237.0592365 | 549.4619765 | 51.46205973 | 85.20907383 | 0 | 341.9138399 |
| GRID- 1-R3C3 | 37948.89855 | 29337.698 | 466.1108442 | 5433.446661 | 1471.582339 | 5909.425076 | 18.73618714 | 11512.26764 |
| GRID- 1-R4C3 | 1783.537418 | 0 | 278.1567203 | 995.9458782 | 213.2421284 | 272.3534771 | 145.0803346 | 526.9021215 |
| GRID- 1-R5C3 | 36087.18461 | 27055.55654 | 1384.764594 | 1341.707566 | 834.4791417 | 5474.453164 | 596.809655 | 10396.41906 |
| GRID- 1-R6C3 | 580.1056292 | 0 | 415.9582789 | 1181.27049 | 174.4947077 | 1345.295015 | 282.488589 | 568.5159308 |
| GRID- 1-R7C3 | 796.1214255 | 745.9987128 | 708.4653805 | 1616.749078 | 301.1569001 | 476.180083 | 543.7117152 | 741.1973912 |
| GRID- 1-R8C3 | 194.2535294 | 0 | 1098.078617 | 1266.1621 | 305.1931705 | 475.6526055 | 1016.822768 | 622.3087833 |
| GRID- 1-R9C3 | 5287.214616 | 9443.250731 | 10937.50847 | 9750.436975 | 9017.172856 | 6390.525192 | 2929.863471 | 7679.422312 |
| GRID- 1-R10C3 | 212.0159863 | 568.9494609 | 691.596358 | 2494.023273 | 469.6188943 | 824.2283298 | 792.9439511 | 864.7677768 |
| GRID- 1-R11C3 | 8038.774088 | 8737.718561 | 8142.425072 | 2505.561348 | 2063.670662 | 5211.230265 | 4095.470336 | 5542.119813 |
| GRID- 1-R12C3 | 2206.347589 | 5073.890981 | 2176.856974 | 4426.650731 | 3414.016145 | 4781.718615 | 1632.688771 | 3387.451813 |
| GRID- 1-R13C3 | 0 | 578.5038809 | 549.5993948 | 1940.926347 | 354.7827416 | 356.4542684 | 496.1559391 | 610.9173269 |
| GRID- 1-R14C3 | 118.7015631 | 367.0067202 | 240.2582325 | 1482.965258 | 148.3829049 | 409.4744585 | 426.7752602 | 456.2233484 |
| GRID- 1-R15C3 | 1183.956782 | 1973.709183 | 122.2974412 | 1438.30469 | 305.3442401 | 1932.17467 | 345.3851554 | 1043.024282 |
| GRID- 1-R1C4 | 52.90664325 | 0 | 419.0523898 | 21.77012397 | 9.573165612 | 0 | 0 | 71.90031023 |
| GRID- 1-R2C4 | 995.5907765 | 0 | 476.7217215 | 366.8924989 | 388.7811533 | 1003.663446 | 205.9261824 | 491.0821067 |
| GRID- 1-R3C4 | 6247.994161 | 1281.176224 | 797.7400932 | 1076.438408 | 833.5494825 | 573.9199371 | 793.0534801 | 1657.695472 |
| GRID- 1-R4C4 | 3007.540073 | 847.1325733 | 357.1526918 | 891.5400047 | 1044.988847 | 1080.634595 | 661.1014514 | 1127.15541 |
| GRID- 1-R5C4 | 1892.12437 | 198.2119672 | 237.0592365 | 854.6577432 | 355.5148483 | 1232.739417 | 329.6871322 | 728.5704549 |
| GRID- 1-R6C4 | 121.5534001 | 0 | 85.79742156 | 1003.785071 | 162.9863015 | 267.8554267 | 309.7090555 | 278.8122987 |
| GRID- 1-R7C4 | 769.8758392 | 0 | 672.4548247 | 1617.768934 | 567.3028348 | 2312.880154 | 510.898533 | 921.5970263 |
| GRID- 1-R8C4 | 1142.612384 | 1412.143273 | 681.6322722 | 1433.022748 | 637.0543898 | 2801.527256 | 938.4792521 | 1292.352695 |
| GRID- 1-R9C4 | 3168.082572 | 3488.377232 | 1081.838905 | 1819.791788 | 878.3706767 | 4144.798149 | 578.4795674 | 2165.676334 |
| GRID- 1-R10C4 | 236.0177414 | 0 | 148.3439111 | 969.520948 | 166.3214539 | 434.4513907 | 260.3923913 | 316.4353103 |
| GRID- 1-R11C4 | 1796.218684 | 4221.532724 | 1426.036887 | 1591.070012 | 523.1362756 | 1756.704331 | 1377.029715 | 1813.103546 |
| GRID- 1-R12C4 | 42069.16607 | 52302.75387 | 32362.96753 | 17201.82587 | 12801.8542 | 31665.44746 | 5656.544038 | 27722.92869 |
| GRID- 1-R13C4 | 5342.123335 | 10170.42659 | 5293.09859 | 10365.01449 | 3618.111201 | 13825.90113 | 1106.971817 | 7103.090319 |
| GRID- 1-R14C4 | 415.9585233 | 0 | 386.6603705 | 2186.22459 | 309.1287278 | 764.0089404 | 418.5049835 | 640.0692559 |
| GRID- 1-R15C4 | 674.4768245 | 746.6486734 | 279.2405331 | 1648.562502 | 310.6936541 | 2540.518605 | 391.1985789 | 941.6196275 |
| GRID- 1-R1C5 | 0 | 0 | 398.0578862 | 0 | 61.52949415 | 8.823366497 | 0 | 66.9158009 |
| GRID- 1-R2C5 | 2884.172788 | 1899.028716 | 3117.711406 | 2492.896865 | 2332.609448 | 10826.55356 | 880.5873153 | 3490.507538 |
| GRID- 1-R3C5 | 19611.28258 | 20034.35778 | 10977.08512 | 3161.937739 | 10239.3532 | 6584.115255 | 3671.620341 | 10611.38996 |
| GRID- 1-R4C5 | 305.2869805 | 0 | 373.8993483 | 555.8246614 | 440.2997673 | 562.7269791 | 549.6330176 | 398.2385597 |
| GRID- 1-R5C5 | 2243.826807 | 1538.560599 | 1095.316642 | 2121.88232 | 1296.608856 | 3919.008768 | 602.8657623 | 1831.152273 |
| GRID- 1-R6C5 | 492.2053534 | 0 | 283.6457079 | 1993.730542 | 268.4638849 | 649.0536098 | 728.3673795 | 630.7807361 |
| GRID- 1-R7C5 | 5164.339527 | 6754.168976 | 3073.205156 | 3979.603625 | 5038.432906 | 16989.43914 | 752.2160401 | 5964.484692 |
| GRID- 1-R8C5 | 9778.756572 | 16306.89906 | 6572.976672 | 2713.170578 | 5032.672893 | 20354.90831 | 1655.123666 | 8916.355576 |
| GRID- 1-R9C5 | 0 | 137.9606249 | 272.9474263 | 646.6527481 | 148.2008467 | 655.325376 | 330.5566234 | 313.0918554 |
| GRID- 1-R10C5 | 161.3777839 | 0 | 153.0287795 | 816.6490734 | 14.15173717 | 51.44471313 | 211.9132022 | 201.2235524 |
| GRID- 1-R11C5 | 739.1860196 | 3425.136071 | 1853.111589 | 2361.639853 | 890.0456468 | 2537.747898 | 459.6423642 | 1752.357966 |
| GRID- 1-R12C5 | 1782.857031 | 2701.080026 | 1772.245166 | 2499.183441 | 1015.421811 | 2950.333895 | 764.9180257 | 1926.576479 |
| GRID- 1-R13C5 | 7156.34044 | 3406.742188 | 432.3727993 | 2551.028667 | 592.3648974 | 3032.098714 | 508.9607135 | 2525.700445 |
| GRID- 1-R14C5 | 1543.997586 | 322.5494191 | 730.3688884 | 4525.287567 | 1324.335942 | 5363.688671 | 496.041355 | 2043.752162 |
| GRID- 1-R15C5 | 1793.482657 | 1517.696866 | 564.5979661 | 2164.655393 | 1185.650157 | 10902.19152 | 387.9919089 | 2645.180131 |
| GRID- 1-R1C6 | 192.7479911 | 0 | 0 | 0 | 0 | 159.3167736 | 0 | 50.2949513 |
| GRID- 1-R2C6 | 477.6421655 | 0 | 0 | 52.62457878 | 95.42331915 | 939.1372889 | 42.81233085 | 229.662743 |
| GRID- 1-R3C6 | 951.5972097 | 663.2587357 | 0 | 261.9538648 | 567.6243419 | 767.6085401 | 390.4150258 | 514.6366625 |
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| GRID- | 1-R7C6 | 397.3419629 | 0 | 0 | 707.7375667 | 323.5035831 | 884.6216129 | 327.4123006 | 377.2308906 |
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| GRID- | 1-R2C16 | 904.5201845 | 0 | 571.4504602 | 0 | 401.9939347 | 1136.309562 | 44.53783275 | 436.9730081 |
| GRID- | 1-R3C16 | 292.2293308 | 355.957391 | 908.306484 | 0 | 132.4431232 | 189.6032603 | 49.67052688 | 275.4585054 |
| GRID- | 1-R4C16 | 408.3584501 | 0 | 688.9742302 | 26.3062007 | 383.1838302 | 939.6821558 | 275.4736824 | 388.8539618 |
| GRID- | 1-R5C16 | 307.1689034 | 0 | 1645.264255 | 0 | 323.8793204 | 919.0583626 | 33.64391694 | 461.2876843 |
| GRID- | 1-R6C16 | 351.6980945 | 1987.618338 | 372.4659184 | 0 | 83.19442709 | 738.4813448 | 0 | 504.7795804 |
| GRID- | 1-R7C16 | 480.7256237 | 4322.666585 | 375.5775101 | 0 | 217.9059188 | 1109.982056 | 0 | 929.5508202 |
| GRID- | 1-R8C16 | 325.2353632 | 0 | 87.42314082 | 0 | 134.3876604 | 335.587024 | 0 | 126.0904177 |
| GRID- | 1-R9C16 | 341.9265717 | 0 | 400.0332225 | 0 | 112.9164064 | 1079.718755 | 69.4430262 | 286.2910544 |
| GRID- | 1-R10C16 | 574.5611948 | 0 | 328.956077 | 94.11902567 | 240.7677879 | 1181.719005 | 218.9516997 | 377.0105712 |
| GRID- | 1-R11C16 | 504.5536629 | 92.07341052 | 296.4067301 | 121.4877034 | 93.31609163 | 631.1367619 | 15.2144108 | 250.5983207 |
| GRID- | 1-R12C16 | 468.0443587 | 1228.399428 | 224.2457718 | 0 | 62.37780817 | 476.2786228 | 0 | 351.3350359 |
| GRID- | 1R13C16 | 402.0178175 | 0 | 133.9047271 | 0 | 67.58777327 | 32.24684831 | 0 | 90.82242507 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| GRID- | 1-R14C16 | 389.9590346 | 0 | 86.96863866 | 0 | 0 | 0 | 0 | 68.13250432 |
| GRID- | 1-R15C16 | 494.8689982 | 0 | 87.56298764 | 0 | 0 | 35.87543025 | 0 | 88.32960436 |
| GRID- | 1-R1C17 | 0 | 0 | 103.7502569 | 0 | 121.0780395 | 133.4066119 | 0 | 51.17640011 |
| GRID- | 1-R2C17 | 2290.339255 | 2644.208479 | 985.5194086 | 637.3827121 | 1605.445516 | 2355.234864 | 291.685649 | 1544.258949 |
| GRID- | 1-R3C17 | 0 | 168.3787783 | 1541.270665 | 0 | 309.864708 | 760.0499605 | 307.7729211 | 441.0480152 |
| GRID- | 1-R4C17 | 1422.425367 | 2057.749081 | 2688.486559 | 1609.990628 | 2500.0953 | 2887.575657 | 342.4362996 | 1929.82212 |
| GRID- | 1-R5C17 | 0 | 191.5173736 | 511.1590006 | 0 | 124.0761904 | 382.1035896 | 0 | 172.6936845 |
| GRID- | 1-R6C17 | 0 | 0 | 173.6911469 | 267.9512279 | 92.80865265 | 1248.981089 | 0 | 254.7759402 |
| GRID- | 1-R7C17 | 0 | 1286.115924 | 10.9094503 | 60.57032393 | 68.99388281 | 63.39121054 | 0 | 212.854335 |
| GRID- | 1-R8C17 | 524.4441403 | 0 | 153.7454944 | 20.64371565 | 396.4973247 | 890.5339988 | 0 | 283.6948683 |
| GRID- | 1-R9C17 | 0 | 0 | 192.1684078 | 123.968846 | 97.66224839 | 785.0616714 | 59.39501074 | 179.7508296 |
| GRID- | 1-R10C17 | 522.3161198 | 0 | 358.0092536 | 727.9672512 | 412.4409799 | 5822.628933 | 516.80804 | 1194.309724 |
| GRID- | 1-R11C17 | 69.35175413 | 0 | 445.4659576 | 321.16641 | 146.1362285 | 2121.017435 | 28.65613801 | 447.3989977 |
| GRID- | 1-R12C17 | 94.62742631 | 449.6167052 | 61.37667089 | 139.3123539 | 19.24936845 | 162.1396481 | 0 | 132.3316993 |
| GRID- | 1-R13C17 | 0 | 0 | 173.6736661 | 6.335285691 | 0.969944432 | 0 | 0 | 25.85412027 |
| GRID- | 1-R14C17 | 0 | 0 | 0 | 0 | 18.85813687 | 15.21106186 | 8.765684461 | 6.119267192 |
| GRID- | 1-R15C17 | 0 | 5221.367028 | 70.01221193 | 0 | 0 | 0 | 0 | 755.9110932 |
| GRID- | 1-R1C18 | 48.85327085 | 0 | 247.5652287 | 0 | 0 | 147.6195239 | 0 | 63.43398432 |
| GRID- | 1-R2C18 | 494.1451817 | 0 | 198.1643401 | 0 | 205.6537852 | 2612.962721 | 102.5763698 | 516.2144734 |
| GRID- | 1-R3C18 | 0 | 1324.203612 | 259.6270168 | 0 | 0 | 120.5268849 | 0 | 243.4795718 |
| GRID- | 1-R4C18 | 110.3921497 | 56.65056093 | 219.4560182 | 0 | 287.8705207 | 259.9316703 | 0 | 133.4715199 |
| GRID- | 1-R5C18 | 228.3163339 | 3545.833744 | 371.1723354 | 0 | 196.976966 | 387.0479673 | 0 | 675.6208468 |
| GRID- | 1-R6C18 | 625.5178764 | 2737.022844 | 681.300136 | 256.5349274 | 508.4244188 | 901.9182399 | 1.439041624 | 816.022253 |
| GRID- | 1-R7C18 | 545.0005289 | 496.8688367 | 717.6777896 | 125.7954541 | 314.6369585 | 1349.793065 | 44.25305754 | 513.4320875 |
| GRID- | 1-R8C18 | 29.57079929 | 0 | 298.9938962 | 10.56692774 | 21.42632041 | 220.5041713 | 0 | 83.00884866 |
| GRID- | 1-R9C18 | 0 | 0 | 284.6246356 | 0 | 1.624579452 | 573.6590965 | 0 | 122.8440077 |
| GRID- | 1-R10C18 | 217.1695598 | 0 | 121.6681305 | 0 | 28.31741923 | 808.6184718 | 0 | 167.9676041 |
| GRID- | 1-R11C18 | 604.9614878 | 0 | 265.0985236 | 0 | 36.84704239 | 1212.845978 | 0 | 302.8217708 |
| GRID- | 1-R12C18 | 281.0101751 | 942.2218008 | 213.3202391 | 35.22613682 | 47.90223971 | 1468.736358 | 0 | 426.916579 |
| GRID- | 1-R13C18 | 6.611339911 | 0 | 159.951197 | 0 | 0 | 333.442335 | 0 | 71.429246 |
| GRID- | 1-R14C18 | 103.6027509 | 0 | 64.0512413 | 0 | 0 | 619.8974322 | 0 | 112.5073126 |
| GRID- | 1-R15C18 | 229.2138663 | 1181.0823 | 0 | 0 | 0 | 12.19110788 | 0 | 203.2124068 |
| GRID- | 1-R1C19 | 0 | 0 | 177.2222791 | 0 | 0 | 0 | 0 | 25.31746085 |
| GRID- | 1-R2C19 | 119.0345187 | 0 | 160.2483715 | 0 | 0 | 497.3603361 | 0 | 110.948999 |
| GRID- | 1-R3C19 | 66.4420118 | 277.5071534 | 253.0192547 | 0 | 0 | 626.0648622 | 0 | 174.7189879 |
| GRID- | 1-R4C19 | 267.4313775 | 3200.574703 | 290.4807211 | 0 | 142.1619354 | 1617.884987 | 0 | 788.3617242 |
| GRID- | 1-R5C19 | 21.82596274 | 3176.591159 | 293.0853681 | 0 | 114.1094691 | 473.4615448 | 0 | 582.7246115 |
| GRID- | 1-R6C19 | 0 | 0 | 233.5281043 | 0 | 26.74474575 | 401.1797289 | 34.09214302 | 99.3635019 |
| GRID- | 1-R7C19 | 164.5336239 | 599.1726262 | 317.9256592 | 0 | 152.2177491 | 374.7826647 | 5.377027896 | 230.5726953 |
| GRID- | 1-R8C19 | 0 | 0 | 146.6482684 | 0 | 64.80266925 | 2279.689643 | 188.2313626 | 382.7673056 |
| GRID- | 1-R9C19 | 260.1208309 | 1428.327291 | 689.3762898 | 0 | 193.4093988 | 1238.309812 | 245.3060451 | 579.2640645 |
| GRID- | 1-R10C19 | 66.03667456 | 0 | 107.7184103 | 271.3152312 | 15.27894895 | 142.9012081 | 0 | 86.17861316 |
| GRID- | 1-R11C19 | 10.25937507 | 0 | 152.7840476 | 0 | 0 | 118.6314436 | 0 | 40.23925453 |
| GRID- | 1-R12C19 | 148.0306077 | 0 | 74.85440802 | 0 | 0 | 472.6500409 | 0 | 99.36212113 |
| GRID- | 1-R13C19 | 453.1192624 | 0 | 114.5359427 | 0 | 0 | 186.8383504 | 0 | 107.7847613 |
| GRID- | 1-R14C19 | 47.57935381 | 0 | 0 | 0 | 0 | 0 | 0 | 6.797048505 |
| GRID- | 1-R15C19 | 179.806152 | 0 | 0 | 0 | 0 | 26.67645335 | 0 | 29.49750621 |
| GRID- | 1-R1C20 | 0 | 0 | 218.7393033 | 0 | 0 | 79.42420997 | 0 | 42.59477483 |
| GRID- | 1-R2C20 | 113.4466553 | 0 | 190.490246 | 0 | 10.75460751 | 346.1597612 | 0 | 94.40729596 |
| GRID- | 1-R3C20 | 1030.884069 | 4192.089512 | 579.3867671 | 0 | 313.6104598 | 7539.881419 | 80.8913269 | 1962.391348 |
| GRID- | 1-R4C20 | 129.5732869 | 7136.28078 | 355.4220874 | 138.3229412 | 343.0419207 | 1965.081155 | 53.02042706 | 1445.819937 |
| GRID- | 1-R5C20 | 1201.313902 | 5827.19525 | 1933.645876 | 871.3712072 | 2645.660563 | 4263.822592 | 475.6723443 | 2459.810938 |
| GRID- | 1-R6C20 | 0 | 0 | 337.0322308 | 0 | 157.272771 | 1965.434739 | 408.9068792 | 409.806537 |
| GRID- | 1-R7C20 | 1486.700272 | 4067.297088 | 759.5619118 | 450.3684882 | 1300.273263 | 4979.343012 | 465.9377501 | 1929.92539 |
| GRID- | 1-R8C20 | 0 | 0 | 243.0202071 | 0 | 95.78743567 | 486.0340595 | 197.886759 | 146.1040221 |
| GRID- | 1-R9C20 | 487.1096853 | 0 | 5457.138908 | 623.1047256 | 1477.911768 | 2671.796757 | 1185.972506 | 1700.432968 |
| GRID- | 1-R10C20 | 268.4881496 | 0 | 289.0472912 | 1726.467336 | 344.8470089 | 1352.297135 | 221.079931 | 600.3179416 |
| GRID- | 1-R11C20 | 0 | 0 | 157.4164734 | 0 | 0 | 399.8697296 | 0 | 79.61229084 |
| GRID- | 1-R12C20 | 292.938671 | 0 | 63.28208379 | 0 | 91.22048485 | 1710.390641 | 0 | 308.2616048 |
| GRID- | 1-R13C20 | 502.1940211 | 0 | 141.369051 | 0 | 0 | 396.6121209 | 0 | 148.5964116 |
| GRID- | 1-R14C20 | 0 | 0 | 70.76388858 | 0 | 0 | 348.1827246 | 0 | 59.84949822 |
| GRID- | 1-R15C20 | 325.1485052 | 487.704393 | 180.4387559 | 0 | 2.771159132 | 123.3613523 | 0 | 159.91769 |
| GRID- | 1-R1C21 | 0 | 0 | 152.137256 | 0 | 0 | 50.61002336 | 0 | 28.96388837 |
| GRID- | 1-R2C21 | 103.5303693 | 0 | 167.2407124 | 0 | 0 | 311.9838521 | 0 | 83.25067985 |
| GRID- | 1-R3C21 | 459.7494216 | 4825.346069 | 1407.332375 | 0 | 275.7849511 | 1071.151592 | 147.2624879 | 1169.517777 |
| GRID- | 1-R4C21 | 301.537611 | 4205.933671 | 1011.233742 | 612.2820728 | 792.4081893 | 2064.299106 | 797.4868741 | 1397.882619 |
| GRID- | 1-R5C21 | 607.3356059 | 3070.842579 | 1296.958273 | 51.45250527 | 1051.957417 | 1468.394367 | 604.4834203 | 1164.488818 |
| GRID- | 1-R6C21 | 332.6327678 | 722.4051451 | 570.4190899 | 254.7235411 | 358.551735 | 2160.589845 | 947.9459217 | 763.895206 |
| GRID- | 1-R7C21 | 8734.53546 | 15747.15304 | 1280.054289 | 1414.360902 | 2802.308138 | 9150.455915 | 1198.391401 | 5761.035293 |
| GRID- | 1-R8C21 | 547.8957949 | 542.2360826 | 432.1105865 | 0 | 222.5697091 | 1186.159091 | 277.5479918 | 458.3597561 |
| GRID- | 1-R9C21 | 1784.75343 | 1032.891297 | 1459.267987 | 1092.543002 | 1963.368182 | 4535.172123 | 845.6930835 | 1816.240756 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GRID- 1-R10C21 | 303.15896 | 0 | 548.5155819 | 763.8600999 | 251.4588687 | 1227.116854 | 436.0464628 | 504.3079669 |
| GRID- 1-R11C21 | 161.2764496 | 0 | 180.7708921 | 0 | 262.6690092 | 1242.048527 | 0 | 263.8234748 |
| GRID- 1-R12C21 | 1393.733281 | 0 | 0 | 314.0883037 | 181.8622569 | 2520.393307 | 0 | 630.0108321 |
| GRID- 1-R13C21 | 348.7014941 | 0 | 166.9085762 | 0 | 0 | 140.692758 | 0 | 93.75751879 |
| GRID- 1-R14C21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GRID- 1-R15C21 | 295.2259311 | 0 | 0 | 0 | 0 | 0 | 0 | 42.17512036 |
| GRID- 1-R1C22 | 0 | 0 | 242.8628795 | 0 | 0 | 153.6130602 | 0 | 56.63940296 |
| GRID- 1-R2C22 | 1175.632893 | 442.207155 | 415.6611045 | 0 | 48.26635623 | 732.5341802 | 0 | 402.0429778 |
| GRID- 1-R3C22 | 2433.669399 | 6127.15204 | 3788.643998 | 1028.687828 | 1583.912285 | 6387.424087 | 1106.617954 | 3208.014408 |
| GRID- 1-R4C22 | 2223.198037 | 3611.219775 | 8996.259822 | 2630.744888 | 4440.894455 | 9674.907731 | 5444.915611 | 5288.875602 |
| GRID- 1-R5C22 | 3679.473406 | 2428.22659 | 2858.907388 | 194.1562615 | 786.3692781 | 5527.455964 | 2605.335994 | 2582.845637 |
| GRID- 1-R6C22 | 462.2393503 | 7194.842224 | 1762.385966 | 256.7480317 | 991.2739129 | 1960.009255 | 2999.011612 | 2232.357952 |
| GRID- 1-R7C22 | 2406.540756 | 4005.680828 | 8895.674998 | 1624.05551 | 3170.883149 | 7145.913642 | 3715.922265 | 4423.523123 |
| GRID- 1-R8C22 | 0 | 0 | 43.73849092 | 0 | 101.1136082 | 749.8597895 | 382.5289429 | 182.4629212 |
| GRID- 1-R9C22 | 0 | 0 | 171.8032149 | 0 | 89.53935113 | 427.6927221 | 90.16421456 | 111.3141813 |
| GRID- 1-R10C22 | 115.9510604 | 0 | 167.6602529 | 0 | 931.066859 | 1411.026835 | 341.7605903 | 423.9235296 |
| GRID- 1-R11C22 | 1761.895305 | 232.0749115 | 687.698128 | 174.1092378 | 2641.744374 | 14236.92209 | 322.0032566 | 2865.205897 |
| GRID- 1-R12C22 | 668.005905 | 0 | 164.8982782 | 0 | 26.27991615 | 1041.682406 | 0 | 271.5522764 |
| GRID- 1-R13C22 | 1510.209832 | 0 | 97.89417135 | 0 | 28.81323747 | 154.0883696 | 0 | 255.8578675 |
| GRID- 1-R14C22 | 0 | 0 | 79.08477427 | 0 | 0 | 0 | 0 | 11.29782151 |
| GRID- 1-R15C22 | 363.0330608 | 0 | 0 | 0 | 0 | 104.6967615 | 0 | 66.818526 |
| GRID- 1-R1C23 | 655.6286428 | 0 | 425.7825179 | 1522.633096 | 0 | 414.239146 | 0 | 431.1832139 |
| GRID- 1-R2C23 | 945.2131481 | 0 | 308.5734033 | 1027.941963 | 0 | 853.4192861 | 0 | 447.8781229 |
| GRID- 1-R3C23 | 799.9866056 | 966.9203014 | 524.4444483 | 0 | 53.13157271 | 1093.137552 | 0 | 491.0884927 |
| GRID- 1-R4C23 | 1242.788588 | 2549.184247 | 806.8825789 | 155.3256181 | 332.0990572 | 2085.456173 | 921.8881469 | 1156.231712 |
| GRID- 1-R5C23 | 1328.995133 | 314.6199004 | 2069.262328 | 384.6410408 | 1026.817883 | 2460.38259 | 2471.628132 | 1436.62057 |
| GRID- 1-R6C23 | 12459.84527 | 14541.41124 | 18638.78535 | 4442.526999 | 8734.815989 | 17729.70464 | 12229.80814 | 12682.41014 |
| GRID- 1R7C23 | 2778.944346 | 1456.210598 | 1263.027939 | 951.2548672 | 917.6255364 | 6706.362528 | 2433.835597 | 2358.179494 |
| GRID- 1-R8C23 | 780.3277494 | 0 | 181.1904326 | 0 | 360.4652835 | 1426.677268 | 38.52216695 | 398.1688663 |
| GRID- 1-R9C23 | 818.4149737 | 0 | 202.8142469 | 0 | 92.57236427 | 870.1188781 | 0 | 283.417124 |
| GRID- 1-R10C23 | 990.9873036 | 0 | 426.5341946 | 0 | 60.72766309 | 2248.551077 | 26.66776668 | 536.2095541 |
| GRID- 1-R11C23 | 750.5499386 | 0 | 246.114318 | 0 | 84.29839739 | 1170.299985 | 0 | 321.6088519 |
| GRID- 1-R12C23 | 923.1656975 | 0 | 0 | 0 | 0 | 929.8919403 | 0 | 264.7224403 |
| GRID- 1-R13C23 | 922.3694994 | 0 | 88.47199196 | 0 | 0 | 512.054354 | 0 | 217.5564841 |
| GRID- 1-R14C23 | 628.3697134 | 0 | 0 | 0 | 0 | 484.9675115 | 0 | 159.0481273 |
| GRID- 1-R15C23 | 883.0228344 | 0 | 0 | 0 | 0 | 581.3741805 | 0 | 209.1995 |

**Table E II, online only.** Gene array data for normal aortic specimens

| *Name* | *Spec normal1* | *Spec normal2* | *Spec normal3* | *Spec normal4* | *Spec normal5* | *Avg normal* |
|---|---|---|---|---|---|---|
| GRID- 1-R1C1 | 18331.00712 | 17716.47928 | 17990.02624 | 4949.542985 | 10485.74474 | 13894.56007 |
| GRID- 1-R2C1 | 0 | 1231.435476 | 3507.593725 | 0 | 566.7180313 | 1061.149446 |
| GRID- 1-R3C1 | 2356.173089 | 0 | 4137.98275 | 0 | 451.0503861 | 1389.041245 |
| GRID- 1-R4C1 | 40841.52351 | 8106.989412 | 15569.79481 | 734.5583699 | 16605.80006 | 16371.73323 |
| GRID- 1-R5C1 | 9705.608636 | 1989.70148 | 3369.15878 | 650.7141278 | 6330.865363 | 4409.209677 |
| GRID- 1-R6C1 | 9214.993928 | 1873.625023 | 5315.505536 | 0 | 5570.420473 | 4394.908992 |
| GRID- 1R7C1 | 69021.03724 | 52906.17329 | 38079.21976 | 23666.47614 | 58174.78465 | 48369.53822 |
| GRID- 1-R8C1 | 21806.22245 | 71270.35822 | 78360.97155 | 120649.4215 | 64733.67044 | 71364.12884 |
| GRID- 1-R9C1 | 938.8788082 | 491.5015123 | 5183.385168 | 83.47160102 | 2613.584283 | 1862.164275 |
| GRID- 1-R10C1 | 0 | 0 | 2666.006405 | 0 | 511.2958444 | 635.46045 |
| GRID- 1-R11C1 | 0 | 0 | 1765.353509 | 0 | 308.1332566 | 414.6973531 |
| GRID- 1-R12C1 | 0 | 0 | 2024.931175 | 0 | 737.3498889 | 552.4562127 |
| GRID- 1-R13C1 | 0 | 0 | 2457.528235 | 0 | 530.2618052 | 597.5580081 |
| GRID- 1-R14C1 | 0 | 0 | 1870.369773 | 0 | 610.3637304 | 496.1467006 |
| GRID- 1-R15C1 | 0 | 0 | 1694.338811 | 0 | 651.7159222 | 469.2109466 |
| GRID- 1-R1C3 | 0 | 33.09052563 | 1121.6553 | 0 | 0 | 230.9491652 |
| GRID- 1-R2C3 | 0 | 0 | 1332.659301 | 0 | 100.4926957 | 286.6303994 |
| GRID- 1-R3C3 | 3475.497845 | 1213.085108 | 755.4098663 | 0 | 4121.672585 | 1913.133081 |
| GRID- 1-R4C3 | 0 | 0 | 183.1149453 | 0 | 1462.443507 | 329.1116905 |
| GRID- 1-R5C3 | 548.2207796 | 4920.128059 | 1053.360727 | 0 | 7282.790856 | 2760.900084 |
| GRID- 1-R6C3 | 637.1339408 | 0 | 837.3050655 | 0 | 1530.739867 | 601.0357746 |
| GRID- 1-R7C3 | 0 | 0 | 1250.958397 | 0 | 912.4997016 | 432.6916196 |
| GRID- 1-R8C3 | 0 | 0 | 3206.728444 | 198.3692661 | 1126.013967 | 906.2223356 |
| GRID- 1-R9C3 | 5502.445685 | 15303.50984 | 29508.78516 | 39251.15403 | 19123.48957 | 21737.87686 |
| GRID- 1-R10C3 | 0 | 372.7250345 | 2592.465877 | 0 | 1242.030546 | 841.4442914 |
| GRID- 1-R11C3 | 0 | 8162.749116 | 3759.885341 | 897.0712836 | 4469.831361 | 3457.90742 |
| GRID- 1-R12C3 | 1278.99348 | 2247.406853 | 5490.176436 | 4584.147708 | 10548.818 | 4829.908496 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| GRID- | 1-R13C3 | 0 | 0 | 586.9563961 | 417.8134553 | 1768.323238 | 554.618618 |
| GRID- | 1-R14C3 | 0 | 0 | 1325.081809 | 0 | 1174.642866 | 499.944935 |
| GRID- | 1-R15C3 | 0 | 0 | 2261.582071 | 0 | 1910.586119 | 834.4336378 |
| GRID- | 1-R1C4 | 0 | 104.6471838 | 1278.645386 | 0 | 0 | 276.6585139 |
| GRID- | 1-R2C4 | 632.1515164 | 1493.789527 | 1709.2995 | 0 | 933.3193689 | 953.7119823 |
| GRID- | 1-R3C4 | 9007.683981 | 690.1179699 | 1720.374295 | 1324.573407 | 2644.453947 | 3077.44072 |
| GRID- | 1-R4C4 | 0 | 644.1259877 | 1635.564676 | 0 | 2504.560903 | 956.8503134 |
| GRID- | 1-R5C4 | 0 | 0 | 1446.904561 | 0 | 2409.709291 | 771.3227704 |
| GRID- | 1-R6C4 | 0 | 0 | 1119.12947 | 0 | 886.1370887 | 401.0533117 |
| GRID- | 1-R7C4 | 0 | 1345.667122 | 987.009101 | 0 | 3146.263176 | 1095.78788 |
| GRID- | 1-R8C4 | 0 | 1260.390449 | 2485.409519 | 429.1997104 | 2271.510026 | 1289.301941 |
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| GRID- | 1-R1C5 | 0 | 725.3709555 | 1185.578244 | 0 | 0 | 382.1898398 |
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| GRID- | 1-R4C5 | 0 | 434.2574075 | 2146.073895 | 0 | 1573.796742 | 830.8256089 |
| GRID- | 1-R5C5 | 323.4980296 | 3880.55288 | 3255.010667 | 578.2561408 | 7487.818054 | 3105.027154 |
| GRID- | 1-R6C5 | 0 | 1444.144575 | 1410.18287 | 0 | 2025.435952 | 975.9526796 |
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| GRID- | 1-R1C6 | 0 | 333.0127386 | 769.9819658 | 5.838043524 | 0 | 221.7665496 |
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| GRID- | 1-R6C6 | 0 | 17776.37453 | 589.6765213 | 16.18918452 | 2114.050388 | 4099.258125 |
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| GRID- | 1-R9C6 | 0 | 0 | 582.4876189 | 236.6684878 | 520.9460218 | 268.0204257 |
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| GRID- | 1-R14C6 | 0 | 1178.461313 | 1770.890907 | 579.2912549 | 2375.532033 | 1180.835102 |
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| GRID- | 1-R1C7 | 0 | 0 | 516.5245818 | 0 | 0 | 103.3049164 |
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| GRID- | 1-R10C7 | 0 | 226.6490258 | 1275.633818 | 1284.203957 | 743.8524002 | 706.0678403 |
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| GRID- | 1-R1C8 | 0 | 15.23495863 | 1222.397082 | 0 | 0 | 247.526408 |
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| GRID- | 1-R9C8 | 0 | 0 | 1429.709484 | 2081.241814 | 1594.416499 | 1021.073559 |
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| GRID- | 1-R1C9 | 0 | 2726.90488 | 1504.415781 | 0 | 0 | 846.264132 |
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| GRID- | 1-R5C14 | 244.9606388 | 178.9282973 | 777.0737209 | 391.9356028 | 0 | 318.579652 |
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| GRID- | 1-R15C16 | 666.6432482 | 1020.137473 | 803.2063527 | 0 | 0 | 497.9974147 |
| GRID- | 1-R1C17 | 0 | 1436.618726 | 509.1413847 | 0 | 0 | 389.1520221 |
| GRID- | 1-R2C17 | 344.9943658 | 3074.761623 | 636.1129451 | 0 | 1058.306432 | 1022.835073 |
| GRID- | 1-R3C17 | 0 | 1891.407286 | 235.6716508 | 206.6501789 | 0 | 466.7458232 |
| GRID- | 1-R4C17 | 1576.783227 | 6275.141406 | 843.2310526 | 269.792139 | 1324.026159 | 2057.794797 |
| GRID- | 1-R5C17 | 407.1462578 | 797.1475249 | 0 | 0 | 0 | 240.8587565 |
| GRID- | 1-R6C17 | 0 | 1054.5719 | 254.6153801 | 0 | 0 | 261.8374561 |
| GRID- | 1-R7C17 | 0 | 250.1062195 | 378.0896366 | 192.1585815 | 0 | 164.0708875 |
| GRID- | 1-R8C17 | 942.9623416 | 2729.433858 | 268.6045957 | 0 | 141.7431154 | 816.5487822 |
| GRID- | 1R9C17 | 5713.453926 | 982.4776813 | 507.9756168 | 57.59374852 | 41.4103473 | 1460.582264 |
| GRID- | 1-R10C17 | 46132.03638 | 5037.365158 | 564.9039522 | 0 | 1278.31594 | 10602.52429 |
| GRID- | 1-R11C17 | 425.5863646 | 3526.111017 | 0 | 287.3890787 | 0 | 847.8172922 |
| GRID- | 1-R12C17 | 908.7531184 | 434.0191704 | 0 | 103.1387689 | 0 | 289.1822115 |
| GRID- | 1-R13C17 | 0 | 400.0245654 | 24.86194469 | 0 | 0 | 84.97730203 |
| GRID- | 1-R14C17 | 0 | 659.7518995 | 1109.317589 | 416.7783412 | 0 | 437.169566 |
| GRID- | 1-R15C17 | 1036.447006 | 943.5106399 | 305.0348444 | 0 | 0 | 456.998498 |
| GRID- | 1-R1C18 | 0 | 657.2412468 | 435.7951506 | 236.6684878 | 0 | 265.940977 |
| GRID- | 1-R2C18 | 0 | 2994.249693 | 698.7729729 | 680.7324367 | 0 | 874.7510205 |
| GRID- | 1-R3C18 | 0 | 1156.897799 | 62.16651941 | 395.0409451 | 0 | 322.8210527 |
| GRID- | 1-R4C18 | 0 | 1092.928077 | 286.7711464 | 294.6348774 | 0 | 334.8668202 |
| GRID- | 1-R5C18 | 0 | 472.1432189 | 0 | 0 | 0 | 94.42864377 |
| GRID- | 1-R6C18 | 585.9998842 | 1122.677174 | 528.1822614 | 212.8608635 | 0 | 489.9440367 |
| GRID- | 1-R7C18 | 26.5301258 | 2050.787922 | 623.8723815 | 162.1402726 | 0 | 572.6661404 |
| GRID- | 1-R8C18 | 936.901248 | 1040.925189 | 679.8292436 | 252.1951993 | 0 | 581.970176 |
| GRID- | 1-R9C18 | 3380.960194 | 187.2727052 | 0 | 57.59374852 | 0 | 725.1653296 |
| GRID- | 1-R10C18 | 3793.679576 | 871.4897248 | 91.01927642 | 101.0685407 | 0 | 971.4514237 |
| GRID- | 1R11C18 | 3333.986719 | 763.6355028 | 621.8322875 | 161.1051585 | 13.11042945 | 978.7340195 |
| GRID- | 1-R12C18 | 2101.555793 | 722.0967222 | 0 | 93.82274202 | 0 | 583.4950514 |
| GRID- | 1-R13C18 | 1136.121176 | 354.741186 | 393.3417674 | 267.7219108 | 0 | 430.3852081 |
| GRID- | 1-R14C18 | 1019.136933 | 373.7696127 | 545.0858968 | 103.1387689 | 341.6780732 | 476.561857 |
| GRID- | 1-R15C18 | 0 | 150.7857734 | 1203.259058 | 4.802929424 | 0 | 271.7695521 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| GRID- | 1-R1C19 | 0 | 1172.987968 | 0 | 248.0547429 | 0 | 284.2085422 |
| GRID- | 1-R2C19 | 0 | 1407.94475 | 300.3717726 | 912.5979951 | 0 | 524.1829035 |
| GRID- | 1-R3C19 | 0 | 1205.516498 | 0 | 1256.255876 | 0 | 492.3544749 |
| GRID- | 1-R4C19 | 0 | 1217.061836 | 617.849247 | 594.8179664 | 0 | 485.9458099 |
| GRID- | 1-R5C19 | 64.591739 | 698.4440519 | 833.7106143 | 2851.366704 | 0 | 889.6226219 |
| GRID- | 1-R6C19 | 0 | 627.1134136 | 0 | 400.2165156 | 0 | 205.4659858 |
| GRID- | 1-R7C19 | 0 | 913.1628955 | 0 | 935.3705053 | 0 | 369.7066802 |
| GRID- | 1-R8C19 | 856.5403926 | 2304.339417 | 726.459962 | 203.5448366 | 206.4665468 | 859.470231 |
| GRID- | 1-R9C19 | 3050.913102 | 1510.484451 | 264.9129971 | 53.45329212 | 0 | 975.9527685 |
| GRID- | 1-R10C19 | 1208.982712 | 460.946074 | 0 | 0 | 0 | 333.9857573 |
| GRID- | 1-R11C19 | 59.7377276 | 918.9538902 | 229.842811 | 0 | 0 | 241.7068858 |
| GRID- | 1-R12C19 | 3817.179155 | 631.810961 | 313.5838095 | 19.29452682 | 0 | 956.3736905 |
| GRID- | 1-R13C19 | 0 | 956.2471631 | 0 | 0 | 0 | 191.2494326 |
| GRID- | 1-R14C19 | 0 | 54.48910626 | 133.861249 | 79.33114462 | 0 | 53.53629997 |
| GRID- | 1-R15C19 | 0 | 219.9600604 | 813.1153803 | 82.43648692 | 0 | 223.1023855 |
| GRID- | 1-R1C20 | 0 | 2313.313015 | 929.2064397 | 410.5676566 | 0 | 730.6174223 |
| GRID- | 1-R2C20 | 0 | 1989.237223 | 948.5387583 | 548.2378319 | 0 | 697.2027627 |
| GRID- | 1-R3C20 | 1759.412196 | 6435.88427 | 444.3441156 | 1018.179633 | 315.8497639 | 1994.733996 |
| GRID- | 1-R4C20 | 0 | 3950.790071 | 2088.271234 | 2836.875107 | 727.1181565 | 1920.610914 |
| GRID- | 1-R5C20 | 1141.514522 | 6564.813314 | 4001.685046 | 1349.416145 | 1514.972458 | 2914.480297 |
| GRID- | 1-R6C20 | 0 | 2503.609499 | 569.7613187 | 524.4302076 | 0 | 719.5602051 |
| GRID- | 1-R7C20 | 1206.157626 | 4351.804237 | 584.1391235 | 860.8422901 | 1046.337304 | 1609.856116 |
| GRID- | 1-R8C20 | 2435.070036 | 1579.481588 | 554.9949245 | 516.1492948 | 0 | 1017.139169 |
| GRID- | 1-R9C20 | 4164.228129 | 2781.882677 | 2478.8035 | 0 | 137.7703681 | 1912.536935 |
| GRID- | 1-R10C20 | 1006.65519 | 2915.967418 | 940.0869406 | 9.978499924 | 245.6415423 | 1023.665918 |
| GRID- | 1-R11C20 | 0 | 1702.809005 | 322.5213638 | 0 | 0 | 405.0660738 |
| GRID- | 1-R12C20 | 6693.013973 | 1735.746815 | 560.6294696 | 0 | 408.2915582 | 1879.536363 |
| GRID- | 1-R13C20 | 1989.887848 | 1117.631434 | 324.1728684 | 0 | 0 | 686.3384301 |
| GRID- | 1-R14C20 | 11.5828526 | 889.2109016 | 176.7032215 | 0 | 0 | 215.4993951 |
| GRID- | 1-R15C20 | 1460.877653 | 1129.561616 | 1226.477269 | 0 | 0 | 763.3833078 |
| GRID- | 1R1C21 | 0 | 2600.853006 | 554.0234512 | 674.5217521 | 0 | 765.879642 |
| GRID- | 1-R2C21 | 0 | 3485.140341 | 176.6060742 | 565.8347716 | 0 | 845.5162373 |
| GRID- | 1-R3C21 | 626.8095356 | 2869.340136 | 2461.316981 | 1053.373513 | 0 | 1402.168033 |
| GRID- | 1-R4C21 | 0 | 3149.397038 | 2928.88708 | 46248.52535 | 35.34763693 | 10472.43142 |
| GRID- | 1-R5C21 | 35.313575 | 4095.076247 | 1451.081896 | 1591.632845 | 611.505032 | 1556.921919 |
| GRID- | 1-R6C21 | 2294.509167 | 4205.068494 | 663.4113448 | 3293.360425 | 478.0563441 | 2186.881155 |
| GRID- | 1-R7C21 | 5100.153438 | 5077.181301 | 902.4909239 | 2439.391293 | 2737.36462 | 3251.316315 |
| GRID- | 1-R8C21 | 601.101253 | 2087.189333 | 396.0618926 | 615.5202484 | 463.8773075 | 832.7500069 |
| GRID- | 1-R9C21 | 44147.49051 | 2698.224795 | 1210.350813 | 468.5340462 | 460.9295508 | 9797.105943 |
| GRID- | 1-R10C21 | 1871.105823 | 2356.99593 | 905.4053438 | 531.6760063 | 0 | 1133.036621 |
| GRID- | 1-R11C21 | 1874.72707 | 3003.046141 | 1131.758623 | 7403.798516 | 557.5221936 | 2794.170509 |
| GRID- | 1-R12C21 | 1534.894906 | 3322.186148 | 35.45100366 | 0 | 283.3989975 | 1035.186211 |
| GRID- | 1-R13C21 | 0 | 1503.28236 | 562.5724162 | 0 | 0 | 413.1709552 |
| GRID- | 1-R14C21 | 0 | 772.3952986 | 314.3609881 | 0 | 0 | 217.3512573 |
| GRID- | 1-R15C21 | 0 | 475.9855561 | 176.5089268 | 0 | 0 | 130.4988966 |
| GRID- | 1-R1C22 | 0 | 4210.780077 | 485.7288782 | 219.0715481 | 0 | 983.1161006 |
| GRID- | 1-R2C22 | 0 | 3654.624674 | 22.53040877 | 52.41817802 | 0 | 745.9146522 |
| GRID- | 1-R3C22 | 561.3702708 | 4356.25133 | 3898.125992 | 530.6408922 | 0 | 1869.277697 |
| GRID- | 1-R4C22 | 1569.283908 | 14561.68831 | 5432.373774 | 851.5262632 | 9908.744086 | 6464.723267 |
| GRID- | 1-R5C22 | 455.4552284 | 4083.946297 | 1115.535019 | 671.4164098 | 315.3081908 | 1328.332229 |
| GRID- | 1-R6C22 | 6356.674643 | 4828.675546 | 3733.072678 | 38051.45679 | 2166.57207 | 11027.29035 |
| GRID- | 1-R7C22 | 3300.753435 | 4802.34729 | 1729.991881 | 1565.754992 | 1469.498496 | 2573.669219 |
| GRID- | 1-R8C22 | 1381.081815 | 2051.441547 | 0 | 532.7111204 | 0 | 793.0468965 |
| GRID- | 1-R9C22 | 2364.699712 | 1952.310469 | 334.4704854 | 168.3509572 | 0 | 963.9663248 |
| GRID- | 1-R10C22 | 2375.53777 | 5935.952828 | 1271.747925 | 129.0166214 | 0 | 1942.451029 |
| GRID- | 1-R11C22 | 23638.0339 | 23867.68851 | 2086.911171 | 84.50671512 | 9220.179388 | 11779.46394 |
| GRID- | 1-R12C22 | 1061.436175 | 1860.589176 | 0 | 0 | 491.5520537 | 682.7154811 |
| GRID- | 1-R13C22 | 101.4205874 | 1726.498328 | 0 | 0 | 0 | 365.583783 |
| GRID- | 1-R14C22 | 1554.824604 | 1565.181252 | 0 | 0 | 0 | 624.0011711 |
| GRID- | 1-R15C22 | 188.0223146 | 1368.128607 | 725.002752 | 0 | 0 | 456.2307347 |
| GRID- | 1-R1C23 | 2594.456252 | 2481.422904 | 902.1023346 | 0 | 0 | 1195.596298 |
| GRID- | 1-R2C23 | 0 | 4317.149898 | 67.12103324 | 455.0775629 | 0 | 967.8696989 |
| GRID- | 1-R3C23 | 0 | 4005.798412 | 1009.741576 | 583.4317113 | 0 | 1119.79434 |
| GRID- | 1-R4C23 | 0 | 6060.544736 | 1066.572764 | 668.3110675 | 0 | 1559.085713 |
| GRID- | 1-R5C23 | 0 | 4981.03735 | 4014.897082 | 471.6393885 | 0 | 1893.514764 |
| GRID- | 1-R6C23 | 2874.910244 | 22047.41028 | 7229.890821 | 127.9815073 | 15614.66686 | 9578.971942 |
| GRID- | 1-R7C23 | 1194.651822 | 6420.233923 | 787.6627799 | 0 | 2314.745002 | 2143.458705 |
| GRID- | 1-R8C23 | 0 | 2699.849694 | 178.7433154 | 181.8074405 | 0 | 612.0800901 |
| GRID- | 1-R9C23 | 0 | 1911.914005 | 0 | 215.9662058 | 0 | 425.5760422 |
| GRID- | 1-R10C23 | 0 | 2722.347831 | 625.7181807 | 0 | 0 | 669.6132023 |
| GRID- | 1-R11C23 | 0 | 4660.82833 | 451.82446 | 92.78762792 | 0 | 1041.088083 |

| | | | | | | |
|---|---|---|---|---|---|---|
| GRID- 1-R12C23 | 0 | 1432.147198 | 349.8197635 | 13.08384222 | 0 | 359.0101608 |
| GRID- 1-R13C23 | 0 | 1202.865347 | 0 | 0 | 0 | 240.5730693 |
| GRID- 1-R14C23 | 0 | 2656.124019 | 306.103465 | 0 | 0 | 592.4454968 |
| GRID- 1-R15C23 | 0 | 1911.303141 | 581.6132929 | 0 | 0 | 498.5832867 |

**Table E III.** Gene array data for aortic occlusive disease specimens

| *Name* | *Spec AOD1* | *Spec AOD2* | *Spec AOD3* | *Spec AOD4* | *Spec AOD5* | *Avg AOD* |
|---|---|---|---|---|---|---|
| GRID- 1-R1C1 | 12489.64206 | 14177.396 | 10456.5521 | 13140.61349 | 22451.21613 | 14543.08396 |
| GRID- 1-R2C1 | 4012.265847 | 681.6121915 | 0 | 528.8755094 | 1500.018114 | 1344.554332 |
| GRID- 1-R3C1 | 2974.10309 | 770.1268028 | 32.33245761 | 594.0287311 | 1466.201569 | 1167.35853 |
| GRID- 1-R4C1 | 50446.03615 | 31350.01408 | 17261.75384 | 13884.16472 | 13706.80097 | 25329.75395 |
| GRID- 1-R5C1 | 5222.143148 | 4652.026935 | 2272.571291 | 7218.082556 | 3201.166213 | 4513.198029 |
| GRID- 1-R6C1 | 9033.774486 | 1975.491848 | 2127.493812 | 2351.406355 | 3317.570534 | 3761.147407 |
| GRID- 1-R7C1 | 62567.03316 | 44883.15352 | 44457.2876 | 47938.32683 | 34171.04495 | 46803.36921 |
| GRID- 1-R8C1 | 24497.28948 | 59589.43642 | 77824.40648 | 75036.89489 | 79670.93796 | 63323.79305 |
| GRID- 1-R9C1 | 3319.941576 | 5020.735898 | 1950.083875 | 9386.998403 | 5690.110278 | 5073.574006 |
| GRID- 1-R10C1 | 0 | 1455.538574 | 0 | 651.2041127 | 1489.476114 | 719.2437603 |
| GRID- 1-R11C1 | 0 | 1986.199466 | 0 | 184.7097323 | 1219.617767 | 678.1053931 |
| GRID- 1-R12C1 | 598.6886006 | 1908.510314 | 8.846739627 | 202.3705207 | 1160.883767 | 775.8599885 |
| GRID- 1-R13C1 | 0 | 2273.282748 | 0 | 205.3622107 | 1170.467404 | 729.8224724 |
| GRID- 1-R14C1 | 788.2758414 | 2467.449892 | 0 | 54.94582334 | 673.6032535 | 796.854962 |
| GRID- 1-R15C1 | 0 | 2599.562536 | 0 | 144.8282824 | 659.4805543 | 680.7742745 |
| GRID- 1-R1C3 | 1629.083747 | 0 | 0 | 55.05174674 | 459.4984999 | 428.7267987 |
| GRID- 1-R2C3 | 947.4399399 | 0 | 0 | 618.5332042 | 1033.705754 | 519.9357797 |
| GRID- 1-R3C3 | 18400.25444 | 2962.758446 | 1456.3634 | 13557.09653 | 1946.057398 | 7664.506042 |
| GRID- 1-R4C3 | 516.2296584 | 133.5522163 | 203.9049041 | 947.5028494 | 1524.58803 | 665.1555317 |
| GRID- 1-R5C3 | 6942.129517 | 2969.443541 | 2383.279979 | 18514.75317 | 3512.845022 | 6864.490246 |
| GRID- 1-R6C3 | 336.4957757 | 250.3932868 | 513.6312948 | 1660.803906 | 1698.873302 | 892.0395131 |
| GRID- 1R7C3 | 0 | 440.7481116 | 0 | 449.3993779 | 1535.014184 | 485.0323347 |
| GRID- 1-R8C3 | 0 | 249.7945265 | 971.9421846 | 669.3686831 | 2007.403201 | 779.7017191 |
| GRID- 1-R9C3 | 7653.728971 | 12695.37183 | 20437.16771 | 17522.871 | 15919.94694 | 14845.81729 |
| GRID- 1-R10C3 | 561.5047601 | 1215.537601 | 3935.351074 | 2013.244626 | 3913.146138 | 2327.75684 |
| GRID- 1-R11C3 | 2230.318397 | 5064.961355 | 3840.548417 | 11975.29339 | 15380.29343 | 7698.282998 |
| GRID- 1-R12C3 | 2706.048596 | 2375.470115 | 6657.567523 | 4016.956146 | 6077.805226 | 4366.769521 |
| GRID- 1-R13C3 | 0 | 1175.665896 | 747.3119262 | 1159.034452 | 2287.287507 | 1073.859956 |
| GRID- 1-R14C3 | 12.62955974 | 1007.178563 | 253.1841852 | 284.1692163 | 1787.727301 | 668.977765 |
| GRID- 1-R15C3 | 1098.440855 | 2109.553648 | 383.1249159 | 669.0844984 | 1388.963779 | 1129.833539 |
| GRID- 1-R1C4 | 892.7430141 | 0 | 0 | 39.59209811 | 493.5572689 | 285.1784762 |
| GRID- 1-R2C4 | 1286.697533 | 0 | 808.8770887 | 1222.407644 | 2022.663299 | 1068.129113 |
| GRID- 1-R3C4 | 16785.34658 | 734.6789177 | 867.3877502 | 4344.920811 | 4391.980414 | 5424.862895 |
| GRID- 1-R4C4 | 2507.794716 | 1991.929093 | 3726.061198 | 2323.383158 | 2554.89212 | 2620.812057 |
| GRID- 1-R5C4 | 185.3150549 | 1373.626251 | 546.9366675 | 2210.817592 | 1702.190714 | 1203.777256 |
| GRID- 1-R6C4 | 0 | 553.0761853 | 0 | 656.1024238 | 939.3122025 | 429.6981623 |
| GRID- 1-R7C4 | 86.99724069 | 1037.756743 | 881.7552174 | 1623.529205 | 2504.267351 | 1226.861152 |
| GRID- 1-R8C4 | 987.5006733 | 1343.688235 | 2172.632547 | 2714.338657 | 2248.605423 | 1893.353107 |
| GRID- 1-R9C4 | 1389.474531 | 3480.612873 | 659.5459338 | 5018.0614 | 3569.809735 | 2823.500895 |
| GRID- 1-R10C4 | 0 | 847.2617831 | 0 | 895.1146886 | 1204.29448 | 589.3341904 |
| GRID- 1-R11C4 | 0 | 1987.861982 | 2725.565087 | 1190.170763 | 3582.489623 | 1897.217491 |
| GRID- 1-R12C4 | 27409.78391 | 15137.74386 | 75390.64805 | 33160.58202 | 30600.5928 | 36339.87013 |
| GRID- 1-R13C4 | 1916.521307 | 7083.583056 | 5743.298841 | 13328.14698 | 11095.00733 | 7833.311503 |
| GRID- 1-R14C4 | 441.5023658 | 1896.703907 | 426.6572101 | 2595.993807 | 1550.010995 | 1382.173657 |
| GRID- 1-R15C4 | 270.5789676 | 1928.89046 | 105.0974567 | 523.2305675 | 727.524372 | 711.0643647 |
| GRID- 1-R1C5 | 1086.933283 | 0 | 0 | 325.1073166 | 813.7033783 | 445.1487957 |
| GRID- 1-R2C5 | 3455.73092 | 1043.890852 | 7999.534209 | 4601.159836 | 6192.219099 | 4658.506983 |
| GRID- 1-R3C5 | 12421.56758 | 9562.727884 | 17665.73986 | 25200.30199 | 18151.45979 | 16600.35942 |
| GRID- 1-R4C5 | 106.272423 | 335.3471851 | 796.5459554 | 1486.174981 | 2538.778973 | 1052.623904 |
| GRID- 1-R5C5 | 1531.772845 | 5319.577813 | 7070.875433 | 5666.614844 | 5450.077049 | 5007.783597 |
| GRID- 1-R6C5 | 0 | 678.2330176 | 556.0322924 | 576.0140035 | 1747.149553 | 711.4857733 |
| GRID- 1-R7C5 | 9665.072667 | 7378.931141 | 18871.45318 | 8585.264229 | 8039.986301 | 10508.1415 |
| GRID- 1-R8C5 | 7612.19383 | 15961.24951 | 26146.70866 | 18137.13369 | 8703.331905 | 15312.12352 |
| GRID- 1-R9C5 | 61.89635031 | 994.1300468 | 0 | 1630.94901 | 1320.172228 | 801.429527 |
| GRID- 1-R10C5 | 0 | 313.5656859 | 0 | 118.2337599 | 1029.882831 | 292.3364554 |
| GRID- 1-R11C5 | 1986.717493 | 1793.535593 | 3109.346155 | 561.2260642 | 1960.969957 | 1882.359052 |
| GRID- 1-R12C5 | 2241.070785 | 4108.444922 | 3601.550691 | 1770.853146 | 5400.484364 | 3424.480782 |
| GRID- 1-R13C5 | 4218.754834 | 3152.794781 | 2944.832999 | 3641.093439 | 2589.688092 | 3309.432829 |
| GRID- 1-R14C5 | 5093.869687 | 3790.277063 | 6440.449074 | 2561.664293 | 3482.345889 | 4273.721201 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| GRID- | 1-R15C5 | 971.7137236 | 3802.596238 | 5862.922146 | 2608.652944 | 2589.60384 | 3167.097778 |
| GRID- | 1-R1C6 | 327.7931747 | 0 | 0 | 0 | 431.8744582 | 151.9335266 |
| GRID- | 1-R2C6 | 0 | 0 | 0 | 473.5240769 | 1176.112271 | 329.9272695 |
| GRID- | 1-R3C6 | 446.5369284 | 419.3806487 | 348.0999723 | 1830.89621 | 2102.291732 | 1029.441098 |
| GRID- | 1-R4C6 | 0 | 524.4153122 | 155.1007676 | 525.274114 | 1898.876419 | 620.7333225 |
| GRID- | 1-R5C6 | 244.6869317 | 819.1901156 | 213.1815365 | 637.1963896 | 1495.82659 | 682.0163126 |
| GRID- | 1-R6C6 | 263.9261528 | 709.3844789 | 2230.419179 | 303.9123037 | 3845.955369 | 1470.719497 |
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| GRID- | 1-R10C19 | 1323.16215 | 0 | 55.61454221 | 76.2984296 | 0 | 291.0150244 |
| GRID- | 1-R11C19 | 56.17852571 | 0 | 190.0804594 | 14.6794324 | 0 | 52.18768349 |
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| GRID- | 1-R3C20 | 2624.524644 | 127.7174881 | 4460.136954 | 691.6745999 | 501.1820521 | 1681.047148 |
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| GRID- | 1-R3C21 | 462.6475285 | 160.0632852 | 1443.081978 | 1322.7326 | 747.2498124 | 827.1550408 |
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| GRID- | 1-R1C22 | 971.0664227 | 0 | 852.6356422 | 259.0576213 | 0 | 416.5519372 |
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| GRID- | 1-R4C22 | 7209.284983 | 6480.357509 | 25604.97596 | 3242.873145 | 14945.19635 | 11496.53759 |
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| GRID- | 1-R1C23 | 1236.459791 | 0 | 1256.780049 | 105.4247796 | 0 | 519.732924 |
| GRID- | 1-R2C23 | 1752.754179 | 0 | 1425.230117 | 50.1663531 | 0 | 645.6301299 |
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| GRID- | 1-R5C23 | 619.7618409 | 2090.877422 | 3148.285385 | 2075.713594 | 3461.735805 | 2279.274809 |
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